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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES **PHS 2006-1**

SOLICITATION OF

THE PUBLIC HEALTH SERVICE

FOR

SMALL BUSINESS INNOVATION RESEARCH CONTRACT PROPOSALS

PROPOSAL RECEIPT DATE

NOVEMBER 4, 2005

Internet: http://grants.nih.gov/grants/funding/sbir.htm

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The Appendices noted above are in Microsoft Word and Adobe Acrobat Reader fillable format.

NOTE: Other software packages for completing these proposals may be available from other sources; however, it is essential that the type size and format specifications are met or the proposal may be returned without review.

DISCLAIMER: Reference to these software packages neither constitutes nor should be inferred to be an endorsement or recommendation of any product, service, or enterprise by the National Institutes of Health, any other agency of the United States Government, or any employee of the United States Government. No warranties are stated or implied.

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

SOLICITATION OF THE PUBLIC HEALTH SERVICE FOR SMALL BUSINESS INNOVATION RESEARCH (SBIR) CONTRACT PROPOSALS

I. GENERAL PROGRAM DESCRIPTION

The Small Business Innovation Research Program was reauthorized by the enactment of the Small Business Reauthorization Act of 2000, (Public Law 106-554) through Fiscal Year 2008. The authorizing SBIR legislation requires two significant programmatic changes:

- Commercialization Plan. All Phase II proposals must include a succinct commercialization plan. See instructions in *Section V.3*. for specific details.
- Data Collection Requirement. Each Phase II offeror will be required to provide information for the Small Business Administration (SBA) Tech-Net Database System. See SBA's Tech-Net website (http://tech-net.sba.gov/) for specific details.

The Public Health Service (PHS), Department of Health and Human Services (HHS), and certain other Federal agencies must reserve 2.5 percent of their current fiscal year extramural budgets for research or research and development (R/R&D) for a Small Business Innovation Research (SBIR) program. The objectives of the SBIR program include stimulating technological innovation in the private sector, strengthening the role of small business in meeting Federal R/R&D needs, increasing private sector commercialization of innovations developed through Federal SBIR R&D, increasing small business participation in Federal R&D, and fostering and encouraging participation by socially and economically disadvantaged small business concerns and women-owned small business concerns in the SBIR program.

The SBIR program consists of three separate phases:

Phase I: Feasibility
$100,000
6 months

The objective of Phase I is to determine the scientific or technical feasibility and commercial merit of the proposed research or R&D efforts and the quality of performance of the small business concern, prior to providing further Federal support in Phase II. Phase I awards normally may not exceed $100,000 for direct costs, indirect costs, and profit (fixed fee) for a period normally not to exceed 6 months.

Phase II: Full R/R&D Effort
$750,000
2 years

The objective of Phase II is to continue the research or R&D efforts initiated in Phase I. Funding shall be based on the results of Phase I and the scientific and technical merit and commercial potential of the Phase II proposal. Phase II awards normally may not exceed $750,000 for direct costs, indirect costs, and negotiated fees for a period normally not to exceed two years. That is, generally, a two-year Phase II project may not cost more than $750,000 for that project. *Phase II proposals may only be submitted upon the request of the Contracting Officer, if not submitted concurrently with the initial Phase I proposal under the Fast-Track procedure (described in Section V). Only one Phase II award may result from a single Phase I SBIR contract.*

Phase III: Commercialization stage without SBIR funds

The objective of Phase III, where appropriate, is for the small business concern to pursue with non-SBIR funds the commercialization objectives resulting from the results of the research or R&D funded in Phases I and II. In some Federal agencies, Phase III may involve follow-on, non-SBIR funded R&D or production contracts for products or processes intended for use by the U.S. Government.

The competition for SBIR Phase I and Phase II awards satisfies any competition requirement of the Armed Services Procurement Act, the Federal Property and Administrative Services Act, and the competition in Contracting Act. Therefore, an agency that wishes to fund an SBIR Phase III project is not required to conduct another competition in order to satisfy those statutory provisions. As a result, in conducting actions relative to a Phase III SBIR award, it is sufficient to state for purposes of a Justification and Approval pursuant to FAR 6.302-5

that the project is a SBIR Phase III award that is derived from, extends, or logically concludes efforts performed under prior SBIR funding agreements and is authorized under 10 U.S.C. 2304(b)(2) or 41 U.S.C. 253(b)(2).

The NIH is interested in developing products and services via the SBIR/STTR program that would improve the health of the American people. In its commitment to also support President Bush's Executive Order 13329, encouraging innovation in manufacturing-related research and development, NIH will expand the focus of our SBIR/STTR program to encourage biomedical research related to advanced processing, manufacturing processes, equipment and systems; or manufacturing workforce skills and protection. This solicitation includes some topic areas that are considered relevant to manufacturing-related R&D. Additional information will be posted on the NIH SBIR/STTR website (http://grants.nih.gov/grants/funding/sbir.htm) and in the NIH Guide for Grants and Contracts as it becomes available. Small businesses may be interested in reading a U.S. Department of Commerce 2004 report, "Manufacturing in America: A Comprehensive Strategy to Address the Challenges to U.S. Manufacturers."

A. PURPOSE OF SOLICITATION

The purpose of this solicitation is to *invite Phase I contract proposals from small business* concerns that have the expertise to contribute to the mission of the awarding components identified below and to provide the opportunity for the submission of Phase II contract proposals concurrently with Phase I (see specific topics listed in Section XII and identified as accepting Fast-Track proposals).

Included are instructions for offerors to prepare contract proposals, a description of the proposal review process, and some conditions of a contract award. *Contract proposals will be accepted only if they respond specifically to a research topic within this solicitation (see* Section XII "Research Topics"*).* Otherwise, proposals will be returned to the offeror(s) without evaluation.

To apply for an SBIR grant rather than a contract, use the *Omnibus Solicitation of the Public Health Service for Small Business Innovation Research Grant Applications (http://grants.nih.gov/grants/funding/sbir.htm#sol)*.

B. AWARDING COMPONENTS

The following awarding components of the PHS are participating in this SBIR Solicitation for Contract Proposals.

National Institutes of Health (NIH)

- National Cancer Institute (NCI)
- National Institute on Drug Abuse (NIDA)
- National Institute of Mental Health (NIMH)
- National Heart, Lung, and Blood Institute (NHLBI)

Centers for Disease Control and Prevention (CDC)

- National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)
- National Center for HIV, STD, and TB Prevention (NCHSTP)
- National Immunization Program (NIP)

C. SBIR PROGRAM ELIGIBILITY

Organizational Criteria: Each organization submitting a proposal under the SBIR program must qualify as a small business concern (defined in Section III). In determining whether an offeror is a small business concern, an assessment will be made of several factors, including whether or not it is independently owned and operated and whether or not it is an affiliate of a larger organization whose employees, when added to those of the offeror organization, exceed 500. In conducting this assessment, all appropriate factors will be considered, including common ownership, common management, and contractual relationships.

In accordance with 13 C.F.R. 121.3, affiliation exists when "… one concern controls or has the power to control the other … control may be affirmative or negative and it is immaterial whether it is exercised so long as the power to control exists." One of the circumstances that would lead to a finding that an organization is controlling or has the power to control another organization involves sharing common office space and/or employees and/or other facilities (e.g., laboratory space). 13 C.F.R. 121.3 also states that control or the power to control exists when "key employees of one concern organize a new concern … and serve as its officers, directors,

principal stockholders, and/or key employees; and one concern is furnishing or will furnish the other concern with subcontracts, financial or technical assistance, and/or other facilities, whether for a fee or otherwise."

Access to special facilities or equipment in another organization is permitted (as in cases where the SBIR awardee has entered into a subcontractual agreement with another institution for a specific, limited portion of the research project). However, *research space occupied by an SBIR contractor organization must be space that is available to and under the control of the SBIR contractor for the conduct of its portion of the project*. Where there is indication of sharing of common employees, a determination will be made on a case-by-case basis of whether or not such sharing constitutes control or the power to control.

Whenever a proposed SBIR project is to be conducted in facilities other than those of the offeror, a letter must be submitted *with* the proposal stating that leasing/rental arrangements have been negotiated for appropriate research space (i.e., space that will be available to and under the control of the SBIR contractor organization).

This letter must be signed by an *authorized official of the organization whose facilities are to be used for the SBIR project.* It also must include a description of the facilities and, if appropriate, equipment that will be leased/rented to the offeror organization.

All SBIR contract proposals will be reviewed with the above considerations in mind. *If it appears that an offeror does not meet eligibility requirements, the PHS will request an eligibility determination of the organization from the cognizant Small Business Administration (SBA) regional office. The evaluation of the proposal for scientific merit will be deferred until the SBA provides a determination*.

Principal Investigator Criteria. The primary employment of the Principal Investigator must be with the offeror at the time of contract award and during the conduct of the proposed project. PHS policy defines a Principal Investigator as the single individual designated in the proposal with responsibility for the scientific and technical direction of the project. Primary employment means that *more than one half of the Principal Investigator's time* is spent in the employ of the small business concern. Employ means that more than one half of the Principal Investigator's salary and benefits are paid by the small business concern. *Primary employment with a small business concern precludes full-time employment at another organization*.

In the event that the Principal Investigator: (1) is a less-than-full-time employee of the small business, (2) is concurrently employed by another organization, or (3) gives the appearance of being concurrently employed by another organization, whether for a paid or unpaid position, at the time of submission of the proposal, *it is essential that documentation be submitted with the proposal to verify his/her eligibility*. If the Principal Investigator also is employed or appears to be employed by an organization other than the offeror (e.g., a university, a nonprofit research institute, or another company), a letter must be provided by the *non-offeror organization* confirming that the Principal Investigator will, if awarded an SBIR contract, become a less-than-half-time employee of such organization and will remain so for the duration of the SBIR project. If the Principal Investigator is employed by a university, the Dean's Office must provide such a letter. If the Principal Investigator is employed by another for-profit organization, the corporate official must sign the letter. This documentation is required for every proposal that is submitted, even one that is a revision of a previously submitted proposal.

Performance Site Criteria. For both Phase I and Phase II, the research or R&D project activity *must be performed in its entirety in the United States (see* Section III. Definitions*)*.

Market Research. *The PHS will not support any market research under its SBIR program*. Neither will it support studies of the literature that will lead to a new or expanded statement of work. Literature searches where the commercial product is a database are acceptable. For purposes of the SBIR program, "market research" is the systematic gathering, recording, computing, and analyzing of data about problems relating to the sale and distribution of the subject of the research project. It includes various types of research, such as the size of potential market and potential sales volume, the identification of consumers most apt to purchase the products, and the advertising media most likely to stimulate their purchases. However, "market research" does not include activities under a research plan or protocol that require a survey of the public as part of the objective of the project to determine the impact of the subject of the research on the behavior of individuals.

II. AGENCY CONTACT FOR INFORMATION

Questions on the administration of an SBIR contract should be directed to the contracting officers listed in Section X. Contracting Officers and Addresses for Mailing and Delivery of Proposals.

Please direct questions of a general nature about the NIH SBIR program to:

Ms. Jo Anne Goodnight
NIH SBIR/STTR Program Coordinator
6705 Rockledge Drive
Rockledge I, Room 3534
Bethesda, MD 20892
Phone: (301) 435-2688 Fax: (301) 480-0146
Email: sbir@od.nih.gov

or

Ms. Kay Etzler
NIH SBIR/STTR Program Analyst
6705 Rockledge Drive
Rockledge I, Room 3522
Bethesda, MD 20892
Phone: (301) 435-2713 Fax: (301) 480-0146
Email: sbir@od.nih.gov

The PHS SBIR Contract Solicitation ***is available in electronic format*** on the NIH "Small Business Funding Opportunities" home page at http://grants.nih.gov/grants/funding/sbir.htm#sol. The Table of Contents includes direct links and cross-references to specific sections of the document. Text searches in the PDF files are possible using the "binocular" icon. The Phase I and Phase II forms have been modified to enable the fields to be filled in directly using Microsoft Word, or Adobe Acrobat Reader software, which is free.

HELP AND INSTRUCTIONS are available for printing and viewing Acrobat files. Information on Fillable PDF Forms is also available. Other software packages for completing an SBIR proposal may be available from other sources.

DISCLAIMER: Reference to these software packages neither constitutes nor should be inferred to be an endorsement or recommendation of any product, service, or enterprise by the National Institutes of Health, any other agency of the United States Government, or any employee of the United States Government. No warranties are stated or implied.

III. DEFINITIONS

Affiliate. This term has the same meaning as set forth in 13 C.F.R. Part 121 – Small Business Size Regulations, §121.103, *"What is affiliation?"*

Child. The NIH Policy on Inclusion of Children defines a child as an individual under the age of 21 years. The intent of the NIH policy is to provide the opportunity for children to participate in research studies when there is a sound scientific rationale for including them, and their participation benefits children and is appropriate under existing Federal guidelines. Thus, children must be included in NIH conducted or supported clinical research unless there are scientific and ethical reasons not to include them.

DHHS Regulations (45 C.F.R. Part 46, Subpart D, Sec.401-409) provide additional protections for children involved as subjects in research, based on this definition: "Children are persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted." Generally, state laws define what constitutes a "child." Consequently, the age at which a child's own consent is required and sufficient to participate in research will vary according to state law. For example, some states consider a person age 18 to be an adult and therefore one who can provide consent without parental permission.

Clinical Research. NIH defines human clinical research as: *(1)* Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies. *(2)* Epidemiologic and behavioral studies. *(3)* Outcomes research and health services research.

> Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.

Clinical Trial. The NIH defines a clinical trial as a prospective biomedical or behavioral research study

of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective.

Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits this definition of a clinical trial.

Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision making for the subject or the test itself imposes more than minimal risk for subjects.

Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

- *Phase I* clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).
- *Phase II* clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.
- *Phase III* studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.
- *Phase IV* studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.
- *NIH-Defined Phase III Clinical Trial*. For the purpose of the Guidelines, an NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Commercialization. The process of developing markets and producing and delivering products for sale (whether by the originating party or by others); as used here, commercialization includes both government and private sector markets.

Consultant. An individual who provides professional advice or services for a fee, but normally not as an employee of the engaging party. In unusual situations, an individual may be both a consultant and an employee of the same party, receiving compensation for some services as a consultant and for other work as a salaried employee. To prevent apparent or actual conflicts of interest, grantees and consultants must establish written guidelines indicating the conditions of payment of consulting fees. Consultants may also include firms that provide paid professional advice or services.

Contract. A mutually binding legal relationship obligating the seller to furnish the supplies or services (including construction) and the buyer to pay for them. It includes all types of commitments that obligate the Government to an expenditure of appropriated funds and that, except as otherwise authorized, are in writing. In addition to bilateral instruments, contracts include (but are not limited to) awards and notices of awards; job orders or task letters issued under basic ordering agreements; letter contracts; orders, such as purchase orders, under which the contract becomes effective by written acceptance or performance; and bilateral contract modifications. Contracts do not include grants and cooperative agreements covered by 31 U.S.C. 6301, et seq.

Essentially Equivalent Work. This term is meant to identify "scientific overlap," which occurs when: (1) substantially the same research is proposed for funding in more than one proposal (contract proposal or grant application) submitted to the same

Federal agency; OR (2) substantially the same research is submitted to two or more different Federal agencies for review and funding consideration; OR (3) a specific research objective and the research design for accomplishing that objective are the same or closely related in two or more proposals or awards, regardless of the funding source.

Feasibility. The extent to which a study or project may be done practically and successfully.

Funding Agreement. Any grant, contract, or cooperative agreement entered into between any Federal agency and any small business concern for the performance of experimental, developmental, or research work, including products or services, funded in whole or in part by the Federal Government.

Human Subjects. A living individual about whom an investigator (whether professional or student) obtains for research purposes (1) data through intervention or interaction with the individual, or (2) identifiable private information. The regulations governing the inclusion of human subjects in research extend to the use of human organs, tissues, and body fluids from individually identifiable human subjects as well as to graphic, written, or recorded information derived from individually identifiable human subjects.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

The use of autopsy materials is governed by applicable state and local law and is not directly regulated by 45 C.F.R. Part 46.

Innovation. Something new or improved, including research for: (1) development for new technologies, (2) refinement of existing technologies, or (3) development of new applications for existing technologies. For purposes of PHS programs, an example of "innovation" would be new medical or biological products, for improved value, efficiency, or costs.

Intellectual Property. The separate and distinct types of intangible property that are referred to collectively as "intellectual property," including but not limited to: patents, trademarks, copyrights, trade secrets, SBIR technical data (as defined in this section), ideas, designs, know-how, business, technical and research methods, and other types of intangible business assets, and including all types of intangible assets either proposed or generated by an SBC as a result of its participation in the SBIR program.

Joint Venture. A joint venture is an association of individuals and/or concerns with interests in any degree or proportion by way of contract, express or implied, consorting to engage in and carry out no more than three specific or limited-purpose business ventures for joint profit over a two year period, for which purpose they combine their efforts, property, money, skill, or knowledge, but not on a continuing or permanent basis for conducting business generally. This means that the joint venture entity cannot submit more than three offers over a two year period, starting from the date of the submission of the first offer. A joint venture may or may not be in the form of a separate legal entity. The joint venture is viewed as a business entity in determining power to control its management.

A contractor and its ostensible subcontractor are treated as joint venturers, and therefore affiliates, for size determination purposes. An ostensible subcontractor is a subcontractor that performs primary and vital requirements of a contract, or of an order under a multiple award schedule contract, or a subcontractor upon which the prime contractor is unusually reliant. All aspects of the relationship between the prime and subcontractor are considered, including, but not limited to, the terms of the proposal (such as contract management, technical responsibilities, and the percentage of subcontracted work), agreements between the prime and subcontractor (such as bonding assistance or the teaming agreement), and whether the subcontractor is the incumbent contractor and is ineligible to submit a proposal because it exceeds the applicable size standard for that solicitation.

For size purposes, a concern must include in its total number of employees its proportionate share of joint venture employees.
http://www.sba.gov/size/part121-fr.html

Key Personnel Engaged on Project. In addition to the principal investigator (PI), Key Personnel are defined as individuals who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not salaries are requested.

Typically, these individuals have doctoral or other professional degrees, although individuals at the masters or baccalaureate level should be included if their involvement meets the definition of Key Personnel. *Consultants should also be included if they meet the same definition.*

Key Personnel must devote measurable effort to the project whether or not salaries are requested. "Zero percent" effort or “as needed” are not acceptable levels of involvement for those designated as Key Personnel.

Principal Investigator. The one individual designated by the offeror to direct the project or program to be supported by the contract. The Principal Investigator is responsible and accountable for the proper conduct of the project or program.

Prototype. A model of something to be further developed that includes designs, protocols, questionnaires, software, devices, etc.

Research or Research and Development (R/R&D). Any activity that is:

- A systematic, intensive study directed toward greater knowledge or understanding of the subject studied.
- A systematic study directed specifically toward applying new knowledge to meet a recognized need.
- A systematic application of knowledge toward the production of useful materials, devices, and systems or methods, including design, development, and improvement of prototypes and new processes to meet specific requirements.

SBIR Technical Data. All data generated during the performance of an SBIR award.

SBIR Technical Data Rights. The rights a small business concern obtains in data generated during the performance of any SBIR Phase I, Phase II, or Phase III award that an awardee delivers to the Government during or upon completion of a Federally-funded project, and to which the Government receives a license.

Small Business Concern. A small business concern is one that, at the time of award of Phase I and Phase II, meets *all* of the following criteria:

1. Is independently owned and operated, is not dominant in the field of operation in which it is proposing, has a place of business in the United States and operates primarily within the United States or makes a significant contribution to the US economy, and is organized for profit.
2. Is (a) at least 51% owned and controlled by one or more individuals who are citizens of, or permanent resident aliens in, the United States, or (b) for SBIR only, it must be a for-profit business concern that is at least 51% owned and controlled by another for-profit business concern that is at least 51% owned and controlled by one or more individuals who are citizens of, or permanent resident aliens in, the United States.
3. Has, including its affiliates, an average number of employees for the preceding 12 months not exceeding 500, and meets the other regulatory requirements found in 13 C.F.R. Part 121. Business concerns are generally considered to be affiliates of one another when either directly or indirectly, (a) one concern controls or has the power to control the other; or (b) a third-party/parties controls or has the power to control both.

Control can be exercised through common ownership, common management, and contractual relationships. The term "affiliates" is defined in greater detail in 13 C.F.R. 121.103. The term "number of employees" is defined in 13 C.F.R. 121.106.

A business concern may be in the form of an individual proprietorship, partnership, limited liability company, corporation, joint venture, association, trust, or cooperative. Further information may be obtained at http://sba.gov/size, or by contacting the Small Business Administration's Government

Contracting Area Office or Office of Size Standards.

Business concerns include, but are not limited to, any individual (sole proprietorship), partnership, corporation, joint venture, association, or cooperative. Further information may be obtained by contacting the Small Business Administration Size District Office at http://www.sba.gov/size/.

Socially and Economically Disadvantaged Individual. A member of any of the following groups: Black Americans; Hispanic Americans; Native Americans; Asian-Pacific Americans; Subcontinent Asian Americans; other groups designated from time to time by the Small Business Administration (SBA) to be socially disadvantaged; or any other individual found to be socially and economically disadvantaged by SBA pursuant to Section 8(a) of the Small Business Act, 15 U.S.C. 637(a).

Socially and Economically Disadvantaged Small Business Concern. A socially and economically disadvantaged small business concern is one that is at least 51% owned and controlled by one or more socially and economically disadvantaged individuals, or an Indian tribe, including Alaska Native Corporations (ANCs), a Native Hawaiian Organization (NHO), or a Community Development Corporation (CDC). Control includes both the strategic planning (as that exercised by boards of directors) and the day-to-day management and administration of business operations. See 13 C.F.R. 124.109, 124.110, and 124.111 for special rules pertaining to concerns owned by Indian tribes (including ANCs), NHOs or CDCs, respectively.

Subcontract. Any agreement, other than one involving an employer-employee relationship, entered into by a Federal Government prime contractor calling for supplies or services required solely for the performance of the prime contract or another subcontract.

United States. The 50 states, the territories and possessions of the Federal Government, the Commonwealth of Puerto Rico, the District of Columbia, the Republic of the Marshall Islands, the Federated States of Micronesia, and the Republic of Palau.

Women-Owned Small Business Concern. A small business concern that is at least 51% owned by one or more women, or in the case of any publicly owned business, at least 51% of the stock is owned by women, and women control the management and daily business operations.

IV. PHASE I PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

A. LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase I proposals should not exceed 25 single-spaced pages, including the cover sheet, abstract, cost breakdown, and all enclosures or attachments. Pages should be of standard size (8 l/2" X 11"), and you should use an Arial, Helvetica, Palatino Linotype or Georgia typeface and a font size of 11 points or larger. Excluded from the 25-pages are cover letters, Human Subjects Research and Vertebrate Animal information, letters of commitment from collaborators and consultants and letters to determine eligibility. Unless specifically solicited by a Contracting Officer, no other appendices may be submitted, and if submitted, they will not be considered in the evaluation of scientific and technical merit.

B. PROPOSAL COVER SHEET

Complete the form identified as Appendix A (MS Word | PDF), and use it as the first page of the proposal. *No other cover sheet should be used*.

- ***Topic Number.*** Provide the appropriate numerical designator of the research topic for which your proposal is being submitted. If your proposal is responsive to a subtopic, provide both the topic and subtopic numbers. (A numerical or alphabetical designator precedes each topic and subtopic.)

- ***Project Title.*** Select a title that reflects the substance of the project. Do not use the title of the topic that appears in the solicitation.

C. ABSTRACT OF RESEARCH PLAN

Complete the form identified as Appendix B (MS Word | PDF), and insert it as the second page of each proposal. Abstracts of successful proposals will be published by NIH and, therefore, should not contain proprietary information. The abstract should include a brief description of the problem or opportunity, specific aims, and a description of the effort. Summarize anticipated results and potential commercial applications of the proposed research.

D. RESEARCH PLAN

Any research proposal involving the collection of information, such as surveys or interviews, of more than nine respondents will require clearance by the U.S. Office of Management and Budget. Therefore, it is not practical to propose such an activity for Phase I, which normally has only a six-month duration.

Beginning on page three of the proposal, discuss in the order indicated the following elements:

1. ***Identification and Significance of the Problem or Opportunity.*** Provide a clear statement of the specific technical problem or opportunity addressed.

2. ***Technical Objectives.*** State the specific objectives of the Phase I effort, including the technical questions it will try to answer to determine the feasibility of the proposed approach.

3. ***Work Plan.*** Provide a detailed plan for the R&D to be carried out, including the experimental design, procedures, and protocols to be used. Address the objectives and the questions stated in *Item 2* above. Discuss in detail the methods to be used to achieve each objective or task. For specific guidance and instructions related to Human Subjects research, please see the section entitled, "Human Subjects Research and Protection from Risk" and the "Human Subjects Research Guidance and Information Supplement."

4. ***Related Research or R&D.*** Describe significant research or R&D that is directly related to the proposal, including any conducted by the Principal Investigator/Project Manager or by the proposing firm. Describe how it relates to the proposed effort and any planned coordination with outside sources. *The Principal Investigator/Project Manager must persuade reviewers of his or her awareness of recent significant research or R&D conducted by others in the same scientific field*.

5. ***Relationship with Future R&D.***

   a. State the results expected from the proposed approach.

   b. Discuss the significance of the Phase I effort in providing a foundation for the Phase II R/R&D effort.

6. ***Potential Commercial Applications.*** Describe why the proposed project appears to have potential commercial applications, and whether and by what means the proposed project appears to have potential use by the Federal Government.

7. ***Key Personnel and Bibliography of Directly Related Work.*** Identify key personnel, including their directly related education, experience, and bibliographic information. Where vitae are extensive, focus on summaries of the most relevant experience or publications. *Provide dates and places of employment* and some information about the nature of each position or professional experience. Curriculum vitae must identify the current or most recent position.

8. ***Salary Rate Limitation.*** Fiscal Year (FY) 2005 is the fifteenth consecutive year for which there is a legislatively mandated provision for the limitation of salary. Specifically, the Consolidated Appropriations Act for FY 2005, Public Law 108-447, restricts the amount of direct salary of an individual under an NIH grant or cooperative agreement (hereafter referred to as a grant) or applicable contract to Executive Level I of the Federal Executive Pay scale. Effective January 1, 2005, the Executive Level I salary level increased to $180,100 per year. It is anticipated that this same limit will apply in FY 2006.

9. ***Consultants.*** Involvement of consultants in the planning and/or research stages of the project is permitted. However, such use must be described in detail and supported by appropriate letters from each individual confirming his/her role in the project.

10. ***Facilities and Equipment.*** Indicate where the proposed research will be conducted. *One of the performance sites must be the offeror organization*. Describe the facilities to be used; identify the location; and briefly indicate their capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Include clinical, computer, and office facilities of the offeror and those of any other performance sites to be used in the project.

    List the most important equipment items already available for this project, noting location and pertinent capabilities of each.

Any equipment and products purchased with Government funds shall be American-made, to the extent possible.

Title to Equipment. Title to equipment purchased with Government funding by the SBIR awardee in relation to project performance vests upon acquisition in the Federal Government. However, the Government may transfer such title to an SBIR awardee upon expiration of the project where the transfer would be more cost-effective than recovery of the property.

E. CURRENT AWARDS AND PENDING PROPOSALS/APPLICATIONS

As the PHS uses both contracts and grants in its SBIR program, a small business concern may not submit both a contract proposal and a grant application for essentially the same project to the same or different awarding component(s) of the PHS. The only exception would be the submission of a grant application after a contract proposal has been evaluated and is no longer being considered for award. A firm that receives a Phase I SBIR contract may be solicited to submit a Phase II grant application and vice versa.

While it is permissible, with proposal notification, to submit identical proposals or proposals containing a significant amount of essentially equivalent work (as defined in this solicitation) for consideration under numerous Federal program solicitations, it is unlawful to enter into contracts or grants requiring essentially equivalent effort.

If there is any question concerning this, it must be disclosed to the soliciting agency or agencies before award.

If a firm elects to submit identical proposals or proposals containing a significant amount of essentially equivalent work under other Federal program solicitations, include a statement in each such proposal indicating the information requested in items 1-10 set forth below.

In addition, provide the information requested in items 1-10 on (a) active funding through contracts, grants, and cooperative agreements from public or private sponsors; (b) contract proposals and grant and cooperative agreement applications pending review or funding; and (c) contract proposals and grant and cooperative agreement applications about to be submitted.

1. Name and address of the funding source.
2. Type of award (contract, grant, cooperative agreement) and identifying number.
3. Title of research project.
4. Name and title of Principal Investigator or Project Manager.
5. Hours per week on the project by the Principal Investigator or Project Manager.
6. Annual costs proposed or awarded.
7. Entire period of support.
8. Date of proposal/application submission or date of award.
9. Title, number, and date of solicitations under which proposals or applications were submitted or awards received.
10. The specific applicable research topic for each SBIR proposal or application submitted or award received. *Specifically identify those projects that are SBIR*.

F. PRIOR SBIR PHASE II AWARDS

If the small business concern has received more than 15 Phase II awards in the prior 5 fiscal years, submit name of awarding agency, date of award, funding agreement number, amount, topic or subtopic title, follow-on agreement amount, source, and date of commitment and current commercialization status for each Phase II. This required proposal information will not be counted toward the proposal page limitations.

G. PROPOSED COST BREAKDOWN

Complete the form identified as Appendix C (Contract Pricing Proposal) (MS Word | PDF). The cost breakdown should appear as the last section of the proposal. *If some items on this form do not apply to the proposed project, they need not be completed*.

- Under “Government Solicitation No.,” enter “PHS 2006-1.”
- If supplies are proposed, provide the quantities and the price per unit.
- Under “Direct Labor,” *list all key personnel by name*. Support personnel may be consolidated into categories or labor classes, e.g., research assistants or data processing clerks.

- If travel is proposed, provide the following details on "Exhibit A – Supporting Schedule": destination(s); duration of trip(s); number of travelers; and cost per trip, broken down by cost elements, e.g., airfare, lodging, and meals.
- If consultants are proposed, provide name(s), rate(s), and number of hours/days.
- If a subcontract is proposed, provide the same type of detailed cost breakdown as required for Appendix C. *Also provide a copy of the subcontractual agreement*.
- Use "Exhibit A – Supporting Schedule" to itemize and justify all major cost elements. If more space is needed, use Page 3 of Appendix C.
- *Normally, at least two-thirds or 67% of the entire research or analytical effort must be carried out by the offeror*, i.e., subcontracts for portions of the scientific/technical effort and consultant fees normally may not exceed 33% of the total cost breakdown.

H. STREAMLINING THE CONTRACTING PROCESS

With the Federal Acquisition Streamlining Act of 1994 and the Federal Acquisition Reform Act of 1996, a number of terms and conditions that previously applied to contracts under $100,000 are no longer applicable. Under the SBIR program, Phase I awards, which normally may not exceed $100,000, will reflect the streamlined contract document.

The NIH has initiated special *"just in time" procedures* that are designed to reduce the administrative burden on offerors without compromising the information needed during the initial evaluation of proposals. Certain documents that would previously have been required for submission with the Phase II proposal will be requested at a later stage in the evaluation process. The following documentation is part of the "just in time" procedures and offerors who elect to submit proposals under the *"Fast-Track" initiative* below are not required to submit this documentation with their initial Phase II business proposal:

- ***Travel Policy.*** The offeror's written travel policy.
- ***Annual Financial Report.*** The offeror's most recent annual financial report.
- ***Total Compensation Plan.*** Salary and fringe benefits of professional employees under service contracts.
- ***Data Substantiating the Costs and Prices Proposed.*** That is, payroll documentation, vendor quotes, invoice prices, etc.

I. REQUIREMENT FOR ADEQUATE ASSURANCE OF PROTECTION OF HUMAN SUBJECTS

The HHS regulations for the Protection of Human Subjects, 45 C.F.R. 46 (as amended), provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the HHS. *The requirement is that an approved assurance of compliance with the regulations must be on file with the Office for Human Research Protections (OHRP), DHHS (*http://www.hhs.gov/ohrp*) before an HHS award can be made.*

Neither an Institutional Review Board (IRB) review nor an OHRP-approved Assurance is required at the time the proposal is submitted or at the time that the proposals are peer reviewed.

Human Subjects Research and Protection from Risk

This information must be submitted with the proposal, but is excluded from the 25-page limitation.

Provided below is a table that presents six possible research scenarios, and links to the instructions for providing information on human subjects protection information and the inclusion of women, minorities, and children specific to each scenario. All research will fall into one of these six scenarios. Which scenario best matches your proposed research depends on your answers to the following five questions:

Question 1: Does your proposed research involve human subjects?

Question 2: Does your proposed human subjects research meet the criteria for one or more of the exemptions in the HHS regulations (45 C.F.R. 46)?

Question 3: Does your proposed research meet the definition of clinical research?

Question 4: Does your proposed research include a clinical trial?

Question 5: Does your proposed research meet criteria for an NIH-Defined Phase III Clinical Trial?

If you answer “Yes” to any of the five questions, proceed to the table below, select the scenario that best matches your responses and then follow the instructions located on the scenario pages.

If you need additional guidance then click on the questions or the column heading in the table below and you will be provided additional information and guidance.

Much of the information on the protection of human subjects that you are required to provide in this section is identical to information that will be required to provide for IRB review.

DECISION TABLE FOR HUMAN SUBJECTS RESEARCH, PROTECTION AND THE INCLUSION OF WOMEN, MINORITIES, AND CHILDREN

	Criteria and Answers to Questions 1 thru 5				
Scenarios with linked instructions	1. Human Subjects Research	2. Exempt from HHS Human Subjects Regulations	3. Clinical Research	4. Clinical Trial	5. NIH-Defined Phase III Clinical Trial
A No Human Subjects	No	N/A	N/A	N/A	N/A
Requirements for Scenario A: - Indicate "No Human Subjects Research" If Human Subjects is "Yes," see Scenarios B-F below.					
B Human Subjects/E-4	Yes	Yes Exemption: 4	No	N/A	N/A
Requirements for Scenario B: - Indicate Exemption 4 (E-4) and include justification that E-4 is appropriate.					
C Human Subjects/ Other Exemptions	Yes	Yes Exemptions: 1, 2, 3, 5, 6	Yes	N/A	N/A
Requirements for Scenario C: - Indicate Exemption number(s) and include justification that the designated exemption(s) is appropriate. - Address "Inclusion of Women and Minorities" - Address "Inclusion of Children"					
D Clinical Research	Yes	No	Yes	No	N/A
Requirements for Scenario D: - Address Protection of Human Subjects - Address "Inclusion of Women and Minorities" - Address "Inclusion of Children" "Targeted/Planned Enrollment Table(s)" for each new study/ protocol (New proposals; Competing Continuation proposals; Competing Supplements) - "Inclusion Enrollment Report Table(s)" (Competing Continuations; Competing Supplements)					
E Clinical Trials	Yes	No	Yes	Yes	No
Requirements for Scenario E: - All requirements in Scenario D - Data and Safety Monitoring Plan - Note: Some trials may require a Data and Safety Monitoring Board, based on risk					
F NIH-Defined Phase III Clinical Trial	Yes	No	Yes	Yes	Yes
Requirements for Scenario F: - All requirements in Scenario E Increased requirements for Inclusion of Women and Minorities in Clinical Research					

J. REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

NIH requires education on the protection of human research participants for all individuals identified as "key personnel" before funds are awarded for contract proposals involving human subjects. For information relating to this requirement, see the following notice (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html), which was published June 5, 2000 in the *NIH Guide for Grants and Contracts*. Prior to award, the selected contractor will be required to provide a description of education completed in the protection of human subjects for all key personnel. While NIH does not endorse programs, there are curricula available that can provide guidance or that can be modified to provide training in this area. See http://ohsr.od.nih.gov/ for computer-based training developed for NIH that can be downloaded at no charge. For information on facilitating education and developing curricula, see http://www.nih.gov/sigs/bioethics.

K. REQUIREMENT FOR ADEQUATE ASSURANCE OF COMPLIANCE WITH THE PHS POLICY ON HUMANE CARE AND USE OF LABORATORY ANIMALS

Instructions and Required Information

This information must be submitted with the proposal, but is excluded from the 25-page limitation.

Create a section heading entitled **"Vertebrate Animals."** Place it immediately following the "Research Plan" section of the proposal (or after Human Subjects Research section, if applicable).

Under the Vertebrate Animals heading, address the following five points. In addition, when research involving vertebrate animals will take place at collaborating site(s) or other performance site(s), provide this information before discussing the five points. Although no specific page limitation applies to this section of the proposal, be succinct.

1. Provide a detailed description of the proposed use of the animals in the work outlined in the Research Design and Methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.
2. Justify the use of animals, the choice of species, and the numbers to be used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.
3. Provide information on the veterinary care of the animals involved.
4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.
5. Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations.

Guidance and Additional Instructions

NIH no longer requires Institutional Animal Care and Use Committee approval of the proposed research before NIH peer review of a proposal (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-064.html).

In August, 2002 NIH announced an IACUC "just-in-time" process for applications submitted for the October 1, 2002 deadline or other deadlines where the applications had a May/June 2003 Council review. The PHS policy requirement that no award may be made without an approved Assurance and without verification of IACUC approval remains in effect. The new policy gave institutions flexibility in the timing of IACUC review relative to the submission of a proposal and the verification of IACUC review. The policy does not require that IACUC approval be deferred. Institutional officials retain the discretion to require IACUC approval prior to NIH peer review in circumstances of their choosing if deemed necessary. As part of the NIH peer review process, the scientific review group will continue to address the adequacy of animal usage and protections in the review of a proposal and will continue to raise any concerns about animal welfare issues. Verification of IACUC approval will be required in a "just-in-time" fashion prior to award.

The PHS *Policy on Humane Care and Use of Laboratory Animals* requires that offeror

organizations proposing to use vertebrate animals file a written Animal Welfare Assurance with the Office of Laboratory Animal Welfare (OLAW), establishing appropriate policies and procedures to ensure the humane care and use of live vertebrate animals involved in research activities supported by the PHS. The PHS policy stipulates that an offeror organization, whether domestic or foreign, bears responsibility for the humane care and use of animals in PHS-supported research activities. This policy implements and supplements the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* and requires that institutions use the *Guide for the Care and Use of Laboratory Animals* as a basis for developing and implementing an institutional animal care and use program. This policy does not affect applicable state or local laws or regulations that impose more stringent standards for the care and use of laboratory animals. All institutions are required to comply, as applicable, with the Animal Welfare Act as amended (7 USC 2131 et sec.) and other Federal statutes and regulations relating to animals. These documents are available from the Office of Laboratory Animal Welfare, National Institutes of Health, Bethesda, MD 20892, (301) 496-7163.

The PHS Policy defines “animal” as “any live, vertebrate animal used or intended for use in research, research training, experimentation or biological testing or for related purposes.”

No PHS award for research involving vertebrate animals will be made to an offeror organization unless that organization is operating in accordance with an approved Animal Welfare Assurance and provides verification that the IACUC has reviewed and approved the proposed activity in accordance with the PHS policy. Proposals may be referred by the PHS back to the IACUC for further review in the case of apparent or potential violations of the PHS policy. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the PHS policy. Foreign offeror organizations applying for PHS awards for activities involving vertebrate animals are required to comply with PHS policy or provide evidence that acceptable standards for the humane care and use of animals will be met.

L. NEEDLE EXCHANGE

It is anticipated that the HHS Fiscal Year 2005 Appropriations Act will continue a restriction on using contract funds to carry out any program of distributing sterile needles or syringes for the hypodermic injection of any illegal drug.

M. BAN ON HUMAN EMBRYO RESEARCH

It is anticipated that the HHS Fiscal Year 2005 Appropriations Act will continue the ban on funding of human embryo research. Currently, contract funds may not be used for: (1) the creation of a human embryo or embryos for research purposes, or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 C.F.R. 46.208(a)(2) and Section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). The term “human embryo or embryos” includes any organism, not protected as a human subject under 45 C.F.R. 46 as of the date of the Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells. Additionally, Federal funds may not be used for cloning of human beings.

N. RESEARCH USING HUMAN EMBRYONIC STEM CELLS

http://stemcells.nih.gov/index.asp

In signing the proposal Cover Sheet, the duly authorized representative of the offeror certifies that if research using human embryonic stem cells is proposed, the offeror will be in compliance with the “Notice of Extended Receipt Date and Supplemental Information Guidance for Applications Requesting Funding that Proposes Research with Human Embryonic Stem Cells” (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-006.html).

V. “FAST-TRACK” INITIATIVE

(Applicable Only to Proposals Submitted to NIH)

The “Fast-Track” initiative is a parallel review option available to those small business concerns (offeror organizations) whose proposals satisfy additional criteria that enhance the probability of the project's commercial success. This initiative is applicable only to NIH and only if an awarding component indicates it is accepting Fast-Track proposals for a particular topic. (Refer to Section XII, “Research Topics,” for notation.)

The Fast-Track initiative is an opportunity for small business concerns to submit both a Phase I and

Phase II proposal for concurrent peer review. This initiative also has the potential to minimize any funding gap between Phase I and Phase II.

Fast-Track Proposal Process

To identify the proposals as Fast-Track, check the box marked "Yes" next to the words "Fast-Track Proposal" shown on the Phase I Proposal Cover Sheet, Appendix A (MS Word | PDF).

The small business concern must submit both a Phase I and a Phase II proposal for concurrent initial peer review and evaluation. The Fast-Track proposal must consist of the following parts:

1. ***Phase I Proposal.*** Prepared in accordance with Section IV. Phase I Proposal Preparation Instructions and Requirements, and addressing all factors stated in the evaluation criteria (Section VII) for Phase I proposals.
2. ***Phase II Proposal.*** Prepared in accordance with Section VI, Fast-Track Phase II Proposal Preparation Instructions and Requirements and addressing all factors stated in the evaluation criteria (Section VII) for Phase II proposals.
3. **Commercialization Plan**
   (formerly Product Development Plan [PDP])

(*Applicable to all Phase II proposals and Phase I/ Phase II Fast-Track proposals*.)

All Phase II proposals *and* Fast-Track proposals must include a succinct Commercialization Plan, formerly referenced as a "Product Development Plan (PDP)." The Commercialization Plan is limited to *15 pages*. Be succinct. There is no requirement for offerors to use the maximum allowable pages allotted to the Commercialization Plan.

Create a section entitled, "Commercialization Plan," and provide a description in each of the following areas:

a. ***Value of the SBIR Project, Expected Outcomes, and Impact.*** Describe, in layperson's terms, the proposed project and its key technology objectives. Clarify the need addressed, specifying weaknesses in the current approaches to meet this need. In addition, describe the commercial applications of the research and the innovation inherent in this proposal. Be sure to also specify the potential societal, educational, and scientific benefits of this work. Explain the non-commercial impacts to the overall significance of the project. Explain how the SBIR project integrates with the overall business plan of the company.

b. ***Company.*** Give a brief description of your company including corporate objectives, core competencies, present size (annual sales level and number and types of employees), history of previous Federal and non-Federal funding, regulatory experience, and subsequent commercialization, and any current products/services that have significant sales. Include a short description of the origins of the company. Indicate your vision for the future, how you will grow/maintain a sustainable business entity, and how you will meet critical management functions as your company evolves from a small technology R&D business to a successful commercial entity.

c. ***Market, Customer, and Competition.*** Describe the market and/or market segments you are targeting and provide a brief profile of the potential customer. Tell what significant advantages your innovation will bring to the market, e.g., better performance, lower cost, faster, more efficient or effective, new capability. Explain the hurdles you will have to overcome in order to gain market/customer acceptance of your innovation.

   Describe any strategic alliances, partnerships, or licensing agreements you have in place to get FDA approval (if required) and to market and sell your product.

   Briefly describe your marketing and sales strategy. Give an overview of the current competitive landscape and any potential competitors over the next several years. (*It is very important that you understand and know the competition*.)

d. ***Intellectual Property (IP) Protection.*** Describe how you are going to protect the IP that results from your innovation. Also note other actions you may consider taking that will constitute at least a temporal barrier to others aiming to provide a solution similar to yours.

e. ***Finance Plan.*** Describe the necessary financing you will require, and when it will be required, as well as your plans to raise the requisite financing to launch your innovation into Phase III and begin the revenue stream. Plans for this financing stage may be demonstrated in one or more of the following ways:

- Letter of commitment of funding.
- Letter of intent or evidence of negotiations to provide funding, should the Phase II project be successful and the market need still exist.
- Letter of support for the project and/or some in-kind commitment, e.g., to test or evaluate the innovation.
- Specific steps you are going to take to secure Phase III funding.

f. ***Production and Marketing Plan.*** Describe how the production of your product/service will occur (e.g., in-house manufacturing, contract manufacturing). Describe the steps you will take to market and sell your product/service. For example, explain plans for licensing, internet sales, etc.

g. ***Revenue Stream.*** Explain how you plan to generate a revenue stream for your company should this project be a success. Examples of revenue stream generation include, but are not limited to, manufacture and direct sales, sales through value added resellers or other distributors, joint venture, licensing, service. Describe how your staffing will change to meet your revenue expectations.

Offerors are *encouraged to seek commitment(s) of funds and/or resources from an investor or partner organization for commercialization* of the product(s) or service(s) resulting from the SBIR contract.

Your Phase III funding may be from any of a number of different sources including, but not limited to: SBIR firm itself; private investors or "angels"; venture capital firms; investment companies; joint ventures; R&D limited partnerships; strategic alliances; research contracts; sales of prototypes (built as part of this project); public offering; state finance programs; non SBIR-funded R&D or production commitments from a Federal agency with the intention that the results will be used by the United States government; or other industrial firms.

Fast-Track proposals that do not contain all parts described above will be redirected for Phase I consideration only.

The Phase I and Phase II proposals will be scored individually.

Fast-Track Phase II proposals may be funded following submission of the Phase I final report, and a determination that the Phase I objectives were met, feasibility was demonstrated, and funds are available.

VI. FAST-TRACK PHASE II PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

A. LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase II proposals generally should not exceed a total of 150 single-spaced pages, including all enclosures and attachments. Pages should be of standard size (8 1/2" x 11") and you should use an Arial, Helvetica, Palatino Linotype or Georgia typeface and a font size of 11 points or larger. Excluded from the page limitation are cover letters and letters from collaborators and consultants.

B. TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Phase II Technical Proposal Cover Sheet** - Use Appendix D (MS Word | PDF).
2. **Table of Contents**
3. **Abstract of the Research Plan** - Use Appendix B (MS Word | PDF). State the broad, long-term objectives and specific aims. Do not include any proprietary information. Briefly and concisely describe the research design and methods for achieving these goals.
4. **Anticipated Results of Phase I Effort** - Briefly discuss and summarize the objectives of your Phase I effort, the research activities to be carried out, and the anticipated results.
5. **Research Plan**
   a. *Detailed Approach and Methodology* - provide an explicit detail description of the Phase II approach. This section should be the major portion of the proposal and must clearly show advancement in the project appropriate for Phase II. Indicate not only what is planned, but also how and where the work will be carried out. List all tasks in a logical sequence to precisely describe what is expected of the contractor in performance of the work. Tasks should contain detail to (1) establish parameters for the project; (2) keep the effort focused on meeting the objectives; (3) describe end products and deliverables; and (4) describe periodic/final reports required to monitor

work progress under the contract. Offerors using Human Subjects or Vertebrate Animals in their research should refer to the specific instructions provided in this solicitation.

b. *Personnel* - List by name, title, department and organization, the extent of commitment to this Phase II effort, and detail each person's qualifications and role in the project. *Provide curricula vitae for all key staff members,* describing directly related education, experience, and relevant publications. Describe in detail any involvement of subcontractors or consultants, and *provide curriculae vitae for all key subcontractor staff. Also, include letters of commitment with proposed consultants confirming the extent of involvement and hourly/daily rate.*

c. *Resources* - List/describe all equipment, facilities and other resources available for this project, including the offeror's clinical, computer and office facilities/equipment at any other performance site that will be involved in this project. Briefly state their capacities, relative proximity and extent of availability to this effort. *(Any equipment specifically proposed as a cost to the contract must be justified in this section as well as detailed in the budget. Equipment and products purchased with Government funds shall be American-made, to the extent possible. Title to the equipment will vest in the Government.)*

d. *Other considerations* - Provide a brief narrative of any unique arrangements, safety procedures in place, animal welfare issues, human subjects, etc. Note: If the research plan includes the use of human subjects or animals, refer to paragraphs IV. I-N of this solicitation for further guidance.

e. *Appendices*

(1) **Work Statement** – The Contracting Officer may require the offeror to develop a Statement of Work similar in format to the sample in Appendix E (MS Word | PDF). Create this from your detailed approach and methodology. It will be incorporated into the final contract document. Do not include proprietary information.

(2) **Commercialization Plan** – Required for ALL Phase II and Fast-Track proposals. Comply with requirements referred to in *Section V.3.*

6. **Summary of Related Activities** - Use Appendix F (MS Word | PDF).

7. **Technical Proposal Cost Information** - Use Appendix C (MS Word | PDF). Delete the fringe benefit costs, indirect costs and fee. Prepare a separate Appendix C for each year of the contract and a summary of the entire project.

8. **Number of Copies** - Submit an original and 9 copies.

C. BUSINESS PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Cover Page** - Use NIH Form 2043, Proposal Summary and Data Record, Appendix G (MS Word | PDF).

2. **Proposed Cost Breakdown** - Use Appendix C (MS Word | PDF). Explain the basis for all costs and submit documentation to support all proposed costs. Prepare a separate Appendix C for each year of the contract and a summary of the entire project.

3. **Number of Copies** - Submit an original and 4 copies.

VII. METHOD OF SELECTION AND EVALUATION CRITERIA

Proposals will be initially screened to determine their compliance with the administrative requirements of this solicitation and their applicability to the research topic selected by the offeror. Using the technical evaluation factors described below in Section VII.B., a peer review panel will evaluate proposals passing the initial screening for technical merit and scientific acceptability, to determine the most promising approaches.

A. EVALUATION PROCESS

Your proposal will be peer reviewed by a panel of scientists selected for their competence in relevant scientific and technical fields. Each peer review panel will be responsible for evaluating proposals for scientific and technical merit. The peer review panel provides a rating, makes specific recommendations related to the scope, direction and/or conduct of the proposed research, and for those proposals

recommended for award, may provide a commentary about the funding level, labor mix, duration of the proposed contract project, vertebrate animal and human subject research issues. The Institute program staff of the awarding component will conduct a second level of review. Recommendations of the peer review panel and program staff are based on judgments about not only the technical merit of the proposed research but also its relevance and potential contributions to the mission and programs of the awarding component. A Phase I or Phase II contract may be awarded only if the corresponding proposal has been recommended as technically acceptable by the peer review panel. *Funding for any/all acceptable proposals is not guaranteed.*

B. TECHNICAL EVALUATION CRITERIA

In considering the technical merit of each proposal, the following factors will be assessed:

FACTORS FOR PHASE I PROPOSALS	WEIGHT
1. The soundness and technical merit of the proposed approach and identification of clear measurable goals (milestones) to be achieved during Phase I. (*Preliminary data are not required for Phase I proposals*.)	40%
2. The qualifications of the proposed Principal Investigator, supporting staff, and consultants.	20%
3. The potential of the proposed research for technological innovation.	15%
4. The potential of the proposed research for commercial application.	15%
5. The adequacy and suitability of the facilities and research environment.	10%

FACTORS FOR PHASE II PROPOSALS	WEIGHT
1. The scientific/technical merit of the proposed research, including adequacy of the approach and methodology, and identification of clear, measurable goals to be achieved during Phase II.	30%
2. The potential of the proposed research for commercialization and the adequacy of the Commercialization Plan.	30%
3. The qualifications of the proposed Principal Investigator, supporting staff and consultants.	25%
4. The adequacy and suitability of the facilities and research environment.	15%

C. PROPOSAL DEBRIEFING

An offeror will be notified if they are no longer being considered for award and is entitled to request one written or one oral debriefing. This debriefing can be requested within three days of receipt of the notification.

D. AWARD DECISIONS

For proposals recommended for award, the awarding component considers the following:

1. Ratings resulting from the scientific/technical evaluation process;
2. Areas of high program relevance;
3. Program balance (i.e., balance among areas of research); and
4. Availability of funds.

The agency is not under any obligation to fund any proposal or make any specific number of contract awards in a given research topic area. The agency may also elect to fund several or none of the proposals received within a given topic area. The SBIR contract projects do not require establishing a competitive range or requesting final proposal revisions before reaching source selection decisions.

VIII. CONSIDERATIONS

A. AWARDS

1. The award instrument will be a contract.
2. A profit or fixed fee may be included in the proposal, as specified in Federal Acquisition Regulation (FAR) Part 15.404-4. The fee will be negotiated as an element of the potential total contract amount over and above allowable costs.
3. Phase I awards will be firm fixed price contracts. Normally, Phase II awards will be cost-plus-fixed-fee contracts.
4. Normally, Phase I contracts may not exceed $100,000. Phase II contracts normally may not exceed $750,000—including direct costs, indirect costs, and negotiated fixed fee.

Approximate number of Phase I contract awards:

AWARDING COMPONENTS		NO. OF AWARDS	ESTIMATED TIME OF AWARD
National Institutes of Health (NIH)	National Cancer Institute (NCI)	47-56	Scientific and Technical Merit Review: May 2006 Anticipated Award Date: July 2006
	National Institute on Drug Abuse (NIDA)	10	Scientific and Technical Merit Review: March 2006 Anticipated Award Date: August 2006
	National Institute of Mental Health (NIMH)	5	Scientific and Technical Merit Review: February - March 2006 Anticipated Award Date: June – July 2006
	National Heart, Lung, and Blood Institute (NHLBI)	7	Scientific and Technical Merit Review: February 2006 Anticipated Award Date: August 2006
Centers for Disease Control and Prevention (CDC)	National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention (NCCDPHP)	3	Scientific and Technical Merit Review: February 2006 Anticipated Award Date: August 2006
	National Center for HIV, STD, and TB Prevention (NCHSTP)	8	Scientific and Technical Merit Review: February 2006 Anticipated Award Date: August 2006
	National Immunization Program (NIP)	4-8	Scientific and Technical Merit Review: February 2006 Anticipated Award Date: June 2006

B. MONTHLY PROGRESS REPORT

Contractors will be required to submit a monthly progress report during Phase I along with their invoice. Phase II reports will be required at intervals stipulated in the terms and conditions of award.

C. FINAL REPORT

Original plus 2 copies

A final report is required of all Phase I and Phase II contractors. It should include a detailed description of the project

objectives, the activities that were carried out, and the results obtained. An original and two copies of this report must be submitted as directed by the Contracting Officer not later than the expiration date of the Phase I contract.

Each Phase II "Fast-Track" contractor must submit semi-annual progress reports. A final report is required no later than the expiration date of the Phase II contract. *All reports (original plus two copies) must be submitted as directed by the Contracting Officer or as specified in the contract.*

D. PAYMENT

The Government shall make payments, including invoice and contract financing payments, by electronic funds transfer (EFT). As a condition to any payment, the contractor is required to register in the Central Contractor Registration (CCR) database on or before the award of a contract. The registration site for the CCR is http://www.ccr.dlis.dla.mil.

Payments on Phase I contracts may be made on a monthly advance basis. Invoices/financing requests submitted for costs incurred under Phase II cost reimbursement contracts will be on a monthly basis unless otherwise authorized by the contracting officer.

E. LIMITED RIGHTS INFORMATION AND DATA

Proprietary Information. Information contained in unsuccessful proposals will remain the property of the offeror. The Government, however, may retain copies of all proposals. Public release of information in any proposal will be subject to existing statutory and regulatory requirements.

The Department of Health and Human Services (HHS) recognizes that, in responding to this solicitation, offerors may submit information that they do not want used or disclosed for any purpose other than for evaluation. Such data might include trade secrets, technical data, and business data (such as commercial information, financial information, and cost and pricing data). The use or disclosure of such information may be restricted if offerors identify it and the Freedom of Information Act (FOIA) does not require its release. For information to be protected, offerors must identify in the Notice of Proprietary Information (on the Proposal Cover Sheet) the page(s) on which such information appears. Any other Notice may be unacceptable to the Government and may constitute grounds for removing the proposal from further consideration without assuming any liability for inadvertent disclosure.

Unless disclosure is required by the FOIA, as determined by FOI officials of the HHS, data contained in those portions of a proposal that have been identified as containing restricted information, in accordance with the Notice of Proprietary Information, shall not be used or disclosed except for evaluation purposes.

The HHS may not be able to withhold data that has been requested pursuant to the FOIA, and the HHS FOI officials must make that determination. The Government is not liable for disclosure if the HHS has determined that disclosure is required by the FOIA.

If a contract is awarded to the offeror as a result of, or in connection with, the submission of a proposal, the Government shall have the right to use or disclose the data to the extent provided by law. Proposals not resulting in a contract remain subject to the FOIA.

Rights to Data Developed Under SBIR Funding Agreement. Rights to data, including software developed under the terms of any funding agreement resulting from a contract proposal submitted in response to this solicitation, shall remain with the awardee. However, the Government shall have the limited right to use such data for internal Government purposes.

(1) Each agency must refrain from disclosing SBIR technical data to outside the Government (except reviewers) and especially to competitors of the Small Business Concern (SBC), or from using the information to produce future technical procurement specifications that could harm the SBC that discovered and developed the innovation.

(2) SBIR agencies must protect from disclosure and non-governmental use all SBIR technical data developed from work performed under an SBIR funding agreement for a period of not less than four years from delivery of the last deliverable under that agreement (either Phase I, Phase II, or Federally-funded SBIR Phase III) unless, subject to (b)(3)of this section, the agency obtains permission to disclose such SBIR technical data from the awardee or SBIR offeror. Agencies are released from obligation to protect SBIR data upon expiration of the protection period except that any such data that

is also protected and referenced under a subsequent SBIR award must remain protected through the protection period of that subsequent SBIR award. For example, if a Phase III award is issued within or after the Phase II data rights protection period and the Phase III award refers to and protects data developed and protected under the Phase II award, then that data must continue to be protected through the Phase III protection period. Agencies have discretion to adopt a protection period longer than four years. The Government retains a royalty-free license for Government use of any technical data delivered under an SBIR award, whether patented or not. This section does not apply to program evaluation.

(3) SBIR technical data rights apply to all SBIR awards, including subcontracts to such awards, that fall within the statutory definition of Phase I, II, or III of the SBIR program, as described in Section 4 of this Policy Directive. The scope and extent of the SBIR technical data rights applicable to Federally-funded Phase III awards is identical to the SBIR data rights applicable to Phases I and II SBIR awards. The data rights protection period lapses only: (i) Upon expiration of the protection period applicable to the SBIR award, or (ii) by agreement between the awardee and the agency.

(4) Agencies must insert the provisions of (1), (2), and (3) immediately above as SBIR data rights clauses into all SBIR Phase I, Phase II, and Phase III awards. These data rights clauses are non-negotiable and must not be the subject of negotiations pertaining to an SBIR Phase III award, or diminished or removed during award administration. An agency must not, in any way, make issuance of an SBIR Phase III award conditional on data rights. If the SBIR awardee wishes to transfer its SBIR data rights to the awarding agency or to a third party, it must do so in writing under a separate agreement. A decision by the awardee to relinquish, transfer, or modify in any way its SBIR data rights must be made without pressure or coercion by the agency or any other party. Following issuance of an SBIR Phase III award, the awardee may enter into an agreement with the awarding agency to transfer or modify the data rights contained in that SBIR Phase III award. Such a bilateral data rights agreement must be entered into only after the SBIR Phase III award, which includes the appropriate SBIR data rights clause, has been signed. SBA must immediately report to the Congress any attempt or action by an agency to condition an SBIR award on data rights, to exclude the appropriate data rights clause from the award, or to diminish such rights.

Copyrights. The awardee may normally copyright and publish (consistent with appropriate national security considerations, if any) material developed with PHS support. The awarding component receives a royalty-free license for the Federal Government and requires that each publication contain an acknowledgement of agency support and disclaimer statement, as appropriate. An acknowledgement shall be to the effect that: "This publication was made possible by contract number _____ from (DHHS awarding component)" or "The project described was supported by contract number _____ from (DHHS awarding component)."

Patents. Small business concerns normally retain the principal worldwide patent rights to any invention developed with Government support. Under existing regulations, 37 CFR 401, the Government receives a royalty-free license for Federal Government use, reserves the right to require the patent-holder to license others in certain circumstances, and requires that anyone exclusively licensed to sell the invention in the United States must normally manufacture it substantially in the United States.

To the extent authorized by 35 U.S.C. 205, the Government will not make public any information disclosing a Government-supported invention for a four year period to allow the awardee a reasonable time to file a patent application, nor will the Government release any information that is part of a patent application.

Information about additional requirements imposed by 37 C.F.R. 401 should be obtained from local counsel or from:

Office of Policy for Extramural Research Administration,
Division of Extramural Inventions and Technology Resources,
National Institutes of Health (NIH)
6705 Rockledge Dr., MSC 7980
Bethesda, MD 20892-7980
(301) 435-0679 (v)
(301) 480-0272 (fax)
jpkim@nih.gov

Inventions must be reported promptly—within two months of the inventor's initial report to the contractor organization—to the Division of Extramural Inventions and Technology Resources, NIH, at the address above. This should be done prior to any publication or presentation of the invention at an open meeting, since failure to report at the appropriate time is a violation of 35 USC 202, and may result in loss of the rights of the small business concern, inventor, and Federal Government in the invention. All foreign patent rights are immediately lost upon publication or other public disclosure unless a United States patent application is already on file. In addition, statutes preclude obtaining valid United States patent protection after one year from the date of a publication that discloses the invention.

The reporting of inventions can be accomplished by submitting paper documentation, including fax, or electronically through the NIH Edison Invention Reporting System. Use of the Edison system satisfies all mandated invention reporting requirements and access to the system is through a secure interactive Web site (https://s-edison.info.nih.gov/iEdison) to ensure that all information submitted is protected. In addition to fulfilling reporting requirements, Edison notifies the user of future time sensitive deadlines with enough lead-time to avoid the possibility of loss of patent rights due to administrative oversight. Edison can accommodate the invention reporting need of all organizations. For additional information about this invention reporting and tracking system, visit the Edison home page cited above or contact Edison via email at Edison@od.nih.gov.

Sharing Biomedical Research Resources. It is the policy of the NIH that unique research resources developed with NIH funding must be shared with the research community. Restricted availability of these resources can impede the advancement of research. Principles and Guidelines for Recipients of NIH Research Grants and Contracts, as published in the Federal Register Notice on December 23, 1999 (http://ott.od.nih.gov/NewPages/RTguide_final.html), provide assistance to determine reasonable terms and conditions for acquiring and disseminating research tools, consistent with the objectives of furthering biomedical research and adhering to the Bayh-Dole Act.

(1) Sharing Research Data. See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html. Offerors submitting proposals that exceed $500,000 per year shall include in the proposal a plan for data sharing or state why data sharing is not possible.

Reviewers will not factor the proposed data-sharing plan into the determination of scientific merit or score. Program staff will be responsible for overseeing the data sharing policy and for assessing the appropriateness and adequacy of the proposed data-sharing plan.

NIH recognizes that data sharing may be complicated or limited, in some cases, by institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the Privacy Rule. As NIH stated in the March 1, 2002 draft data sharing statement (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-035.html), the rights and privacy of people who participate in NIH-sponsored research must be protected at all times. Thus, data intended for broader use should be free of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual subjects. When data sharing is limited, offerors should explain such limitations in their data sharing plans.

For more information on data sharing, please see our website at http://grants.nih.gov/grants/policy/data_sharing/.

(2) Sharing Model Organisms. All proposals where the development of model organisms is anticipated are to include a description of a specific plan for sharing and distributing unique model organism research resources or state appropriate reasons why such sharing is restricted or not possible. Unlike the NIH Data Sharing Policy, the submission of a model organism sharing plan is not subject to a cost threshold of $500,000 or more in direct costs in any one year. The adequacy of plans for sharing model organisms will be considered by the reviewers when a competing proposal is evaluated. Reviewers will be asked to describe their assessment of the sharing plan in an administrative note and will not include their assessment in the overall score. For additional information on this policy, see the NIH Model Organism for Biomedical Research Website at: http://www.nih.gov/science/models/ and NIH GUIDE Notice OD-04-042: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html.

Royalties. If royalties exceed $1,500, you must provide the following information on a separate page for each separate royalty or license fee:

1. Name and address of licensor.
2. Date of license agreement.
3. Patent numbers.
4. Patent application serial numbers, or other basis on which the royalty is payable.
5. Brief description (including any part or model number of each contract item or component on which the royalty is payable).
6. Percentage or dollar rate of royalty per unit.
7. Unit price of contract item.
8. Number of units.
9. Total dollar amount of royalties.
10. If specifically requested by the Contracting Officer, a copy of the current license agreement and identification of applicable claims of specific patents (see FAR 27.204 and 31.205-37).

F. PERFORMANCE OF RESEARCH AND ANALYTICAL WORK

In Phase I projects, normally a minimum of two-thirds or 67% of the research or analytical effort must be performed by the small business concern.

In Phase II projects, normally a minimum of one-half or 50% of the research or analytical effort must be performed by the small business concern.

The Contracting Officer must approve deviations from these requirements in writing.

Contractor Commitments. Upon entering into a contract, the contractor agrees, in accordance with the terms and conditions of the contract, to accept certain legal commitments embodied in the clauses of Phase I and Phase II contracts. The following list illustrates the types of clauses to which a contractor is bound. This list is not exhaustive. Copies of complete terms and conditions are available upon request.

Clauses That Apply to Contracts *NOT* Exceeding $100,000

1. ***Standards of Work.*** Work performed under the contract must conform to high professional standards.
2. ***Inspection.*** Work performed under the contract is subject to Government inspection and evaluation at all times.
3. ***Termination for Convenience.*** The Government may terminate the contract at any time for convenience if it deems termination to be in its best interest, in which case the contractor will be compensated for work performed and for reasonable termination costs.
4. ***Disputes.*** Any dispute concerning the contract that cannot be resolved by agreement shall be decided by the contracting officer with right of appeal.
5. ***Equal Opportunity.*** The contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin.
6. ***Affirmative Action for Veterans.*** The contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran or veteran of the Vietnam era.
7. ***Affirmative Action for Handicapped.*** The contractor will not discriminate against any employee or applicant for employment because he or she is physically or mentally handicapped.
8. ***Gratuities.*** The Government may terminate the contract if any gratuities have been offered to any representative of the Government to secure the contract.
9. ***American-made Equipment and Products.*** When purchasing equipment or products under an SBIR contract award, the contractor shall purchase only American-made items whenever possible.

Clauses That Apply to Contracts Exceeding $100,000

In addition to the foregoing clauses, the following clauses apply to contracts expected to exceed $100,000.

10. ***Examination of Records.*** The Comptroller General (or a duly authorized representative) shall have the right to examine any directly pertinent records of the contractor involving transactions related to this contract.
11. ***Default.*** The Government may terminate the contract for default if the contractor fails to

perform the work described in the contract and such failure is not the result of excusable delays.

12. ***Contract Work Hours.*** The contractor may not require an employee to work more than eight hours a day or forty hours a week unless the employee is compensated accordingly (i.e., overtime pay).

13. ***Covenant Against Contingent Fees.*** No person or agency has been employed to solicit or secure the contract upon an understanding for compensation except bona fide employees or commercial agencies maintained by the contractor for the purpose of securing business.

14. ***Patent Infringement.*** The contractor shall report each notice or claim of patent infringement based on the performance of the contract.

G. ADDITIONAL INFORMATION

1. This solicitation is intended for informational purposes and reflects current planning. If there is any inconsistency between the information contained herein and the terms of any resulting SBIR contract, the terms of the contract are controlling.

2. Prior to award of an SBIR contract, the Government may request the offeror to submit certain organizational, management, personnel and financial information to assure responsibility of the offeror to receive an award.

3. The Government is not responsible for any expenditures of the offeror in advance and in anticipation of an award. In a cost reimbursement contract, reimbursement of costs by the Government may be made only on the basis of costs incurred by the contractor after award and during performance.

4. This solicitation is not an offer by the Government and does not obligate the Government to make any specific number of awards. Awards under this program are contingent upon the scientific/technical merit of proposals and the availability of funds.

5. The SBIR contract program is not intended as a mechanism to invite unsolicited proposals. Unsolicited SBIR contract proposals shall not be accepted under the SBIR program in either Phase I or Phase II.

6. If an award is made pursuant to a proposal submitted in response to this SBIR solicitation, the contractor will be required to certify that he or she has not previously been, nor is currently being, paid for essentially equivalent work by any agency of the Federal Government.

7. Prior to award of a contract, the contractor will be required to provide a Data Universal Numbering System (DUNS) number. A DUNS number may be obtained immediately, at no charge, by calling Dun and Bradstreet on (800) 333-0505.

IX. INSTRUCTIONS FOR PROPOSAL SUBMISSION

A. RECEIPT DATE

The deadline for receipt of all contract proposals submitted in response to this solicitation is:
5:00 p.m., Eastern Standard Time
Friday, November 4, 2005

Any proposal received at the offices designated below after the exact time specified for receipt will not be considered unless it is received before award is made and:

1. It was sent by registered or certified mail not later than the fifth calendar day prior to the date specified for receipt of proposals;

2. It was sent by mail or hand-delivered and it is determined by the Government that the late receipt was due primarily to mishandling by the Government after receipt at the Government installation;

3. It was transmitted through an electronic commerce method authorized by the solicitation and was received at the initial point of entry to the Government infrastructure not later than 5:00 p.m. one working day prior to the date specified for receipt of proposals;

4. It is the only proposal received, or;

5. It is received in the office designated for receipt of proposals on the first workday on which normal Government processes are resumed following an emergency or anticipated event that interrupts normal Government processes so that proposals cannot be received by the exact time specified in the solicitation.

Despite the specified receipt date above, a proposal received after that date may be considered if it offers significant costs or technical advantages to the Government and it was received before proposals were distributed for evaluation, or within 5 calendar days after the exact time specified for receipt, whichever is earlier.

B. NUMBER OF COPIES

For Phase I, submit the original and 5 copies of each proposal. The Principal Investigator and a corporate official authorized to bind the offeror must sign the original. The 5 copies of the proposal may be photocopies of the original.

For Phase II, see instructions under paragraph VI.

C. BINDING AND PACKAGING OF PROPOSAL

Send all copies of a proposal in the same package. Do not use special bindings or covers. Staple the pages in the upper left corner of each proposal.

X. CONTRACTING OFFICERS AND ADDRESSES FOR MAILING OR DELIVERY OF PROPOSALS

Any small business concern that intends to submit an SBIR contract proposal under this solicitation should provide the appropriate contracting officer(s) with early, written notice of its intent, giving its name, address, telephone, and topic number(s). If a topic is modified or canceled before this solicitation closes, only those companies that have expressed such intent will be notified.

A. NATIONAL INSTITUTES OF HEALTH (NIH)

National Cancer Institute (NCI)

Ms. Mary Landi-O'Leary
Phone: (301) 435-3807
Fax: (301) 480-0309
Email: ml186r@nih.gov

Proposals to the NCI, if mailed through the U.S. Postal Service, must be addressed as follows:

Ms. Mary Landi-O'Leary
Contracting Officer
Research Contracts Branch,
National Cancer Institute
6120 Executive Blvd., EPS Room 6044
Bethesda, MD 20892-7222 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NCI*.

National Institute on Drug Abuse (NIDA)

Ms. Nancy A. Hurd
Phone: (301) 443-6677
Fax: (301) 443-7595
Email: nhurd@nida.nih.gov

Proposals to the NIDA must be mailed or delivered to:

Ms. Nancy A. Hurd
Contracting Officer, Contracts Management Branch
National Institute on Drug Abuse
6101 Executive Boulevard
Room 260, MSC 8402
Bethesda, Maryland 20892-8402 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIDA*.

National Institute of Mental Health (NIMH)

Mr. David Eskenazi
Phone: (301) 443-2696
Fax: (301) 443-0501
Email: de5d@nih.gov

Proposals mailed to the NIMH must be addressed to:

Mr. David Eskenazi
Contracting Officer
Chief, Contracts Management Branch
National Institute of Mental Health
6001 Executive Boulevard
Room 8154, MSC 9661
Bethesda, Maryland 20892-9661*

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIMH*.

National Heart, Lung, and Blood Institute (NHLBI)

Mr. John Taylor
Phone: (301) 435-0327
Fax: (301) 480-3338
E-mail: taylorjc@nhlbi.nih.gov

Proposals to the NHLBI, if mailed through the U.S. Postal Service, must be addressed as follows:

Review Branch
Division of Extramural Affairs
National Heart, Lung, and Blood Institute
6701 Rockledge Drive
Room 7091
Bethesda, MD 20892-7924*

*Change the zip code to 20817 if hand-delivered or delivered by an express or other courier service to the NHLBI.

B. CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

Mr. Curt Bryant
Phone: (770) 488-2806
Fax: (770) 488-2828
Email: ckb9@cdc.gov

Proposals to the NCCDPHP, NCHSTP, and NIP must be mailed or delivered to:

Mr. Curt Bryant
CDC Small Business Program Manager
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

XI. SCIENTIFIC AND TECHNICAL INFORMATION SOURCES

Health science research literature is available at academic and health science libraries throughout the United States. Information retrieval services are available at these libraries and Regional Medical Libraries through a network supported by the National Library of Medicine. To find a Regional Medical Library in your area, visit http://nnlm.gov/ or contact the Office of Communication and Public Liaison at publicinfo@nlm.nih.gov, (301) 496-6308.

Other sources that provide technology search and/or document services include the organizations listed below. They should be contacted directly for service and cost information.

National Technical Information Service
1-800-553-6847
http://www.ntis.gov

National Technology Transfer Center
Wheeling Jesuit College
1-800-678-6882
http://www.nttc.edu/

Regional Technology Transfer Centers
1-800-472-6785
http://www.ctc.org/NewFiles/RTTCs.html

XII. RESEARCH TOPICS

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE (NCI)

The NCI is the Federal Government's principal agency established to conduct and support cancer research, training, health information dissemination, and other related programs. As the effector of the National Cancer Program, the NCI supports a comprehensive approach to the problems of cancer through intensive investigation in the cause, diagnosis, prevention, early detection, treatment, rehabilitation from cancer, and the continuing care of cancer patients and families of cancer patients. To speed the translation of research results into widespread applications, the National Cancer Act of 1971 authorized a cancer control program to demonstrate and communicate to both the medical community and the general public the latest advances in cancer prevention and management.

Total costs for the following NCI contract topics are capped at a maximum of $100,000 for Phase I and $750,000 total costs for Phase II.

This solicitation invites proposals in the following areas:

196 Antibody Array for Cancer Detection

(Fast-Track proposals will be accepted.)

The purpose of this initiative is to develop an antibody array in collaboration with the NCI's Early Detection Research Network (EDRN). It is anticipated that the collaboration will provide sets of antigens by the EDRN investigators and permit the development, production and dissemination of antibody microarray technologies for the research community engaged in research focused on early detection and risk assessment of cancer. The specific objectives are:

- Prepare and purify biomarker-specific antibodies in the form of recombinant antibodies or monoclonal antibodies (mAb).
- Develop and/or improve methodologies for quantitative measurements of the bound antigens on Ab microarrays.

- Perform initial validation studies in collaboration with EDRN using the antibody microarrays.

Currently there is no single marker or a combination of biomarkers that has a sufficient sensitivity and specificity to diagnose asymptomatic cancer or early stage cancer. However, recent developments in gene and proteomic profiling of precancerous and cancerous lesions suggest that patterns of markers may be used to distinguish cancer and non-cancer with high sensitivity and specificity (95-100%). Antibody microarrays will provide a fast, reliable, high-throughput, sensitive, and quantitative detection tool of multiple differentially expressed antigens (annotated proteins and post-translational modified proteins) from a limited amount of sample (e.g. 20ul of serum) obtained through a minimally invasive method. Involvement of biotech, via SBIR mechanism, with high-throughput technologies will further strengthen the EDRN efforts in early detection and in dissemination of these technologies.

Phase I Activities and Expected Deliverable: Establish the proof of principle – develop a microarray for detection of 3 markers, which will be selected by the EDRN, and demonstrate that the tiled antibodies perform as well or better than a conventional ELISA in detection of these markers in serum of cancer patients.

Phase II Activities: 1) Development of an antibody array with a capability to simultaneously detect 50 biomarkers; 2) Validate the antibody array in a population based study in collaboration with EDRN investigators. At least 1000 microarrays will be printed and tested by EDRN investigators.

197 Early Detection Research Network Bioinformatics Research Program (EDRN-BRP)

(Fast-Track proposals will be accepted.)

The purpose of this initiative is to support the development of software for analysis and evaluation of cellular signatures for earlier cancer detection in prevention research. The work will be performed in collaboration with the NCI Early Detection Research Network (EDRN) (http://www.cancer.gov/edrn). The objectives are:

1) Develop analytical methods for proteomic and genomic data analysis

- pre-analytical data processing algorithms for time-of-flight (TO) Mass Spectrometer (MS) data and genomic expression data

- protein biomarker identification via innovative data mining and pattern recognition methods such as the classification tree, boosting, support vector machines, artificial neural networks, cluster analysis, etc.

2) Development of algorithms to improve diagnostics by applying:

- algorithms for longitudinal or cross-sectional data in order to classify patients according to the relevant disease states using surface-enhanced laser diffraction/ Matrics-Assisted (SELDI/MALDI) profiling data; gene expression analysis;

- algorithms to patient data for early detection of cancer;

- validating the clinical utility of algorithms to differentiate cancer types;

- validation of the algorithms through the analysis of simulated data and comparison with well established results.

The data for both the development and validation of algorithms will come from the various laboratories of the Early Detection Research Network. The EDRN is comprised of 18 biomarker development laboratories (BDLs), nine clinical and epidemiology centers (CECs), three biomarker validation laboratories (BVLs), and a central data management and coordinating center (DMCC). The successful awardees will become Associate Members of EDRN and serve on its committees and subcommittees. The awardees will closely work with the DMCC and follow the policies and procedures of the EDRN.

The proposed initiative fulfills the needs of and provides a unique opportunity for the awardees to collaborate with investigators of the Early Detection Research Network, a NCI flagship program. This type of mechanism is particularly suited to an area such as informatics which can assist in analyzing some important research questions in new emerging proteomics and genomics data arising from study on precancerous and cancerous lesions. Data mining and bioinformatics tools developed through the initiative have the potential for commercialization, a major objective of the SBIR mechanism.

Phase I Activity and Expected Deliverables: Development of data mining, algorithms and analytical tools.

Phase II Activity and Expected Deliverables: Cross-comparison and Validation of data mining, algorithms and analytical tools.

204 Plant Genomic Models for Establishing Physiological Relevance of Bioactive Components as Cancer Protectants

(Fast-Track proposals will not be accepted.)

Although considerable evidence points to enhanced consumption of whole grains, fruits and vegetables as deterrents to cancer, there are numerous conflicting results. Part of the discrepancies about the health benefits of foods may arise from variation in the content and/or bioavailability of specific bioactive components. While the scientific community lumps foods by classes, there is recognized variation within individual species and varieties of grains, fruits and vegetables. Recent advances in plant genomics provide an exceptional opportunity to evaluate the physiological significance of bioactive components and the food matrix for their overall influence on cancer prevention and tumor behavior. Using these technologies, products of individual genes can be eliminated or enhanced. For example, the content and availability of specific carbohydrates, flavonoids, carotenoids, polyphenols, etc., can be increased or decreased by genomic manipulation. This would allow content, speciation, and molecular targets involved in cancer processes to be examined.

The purpose of this initiative is to develop and market new plant genomic and genetic resources for evaluating food bioactive components and for evaluating the food matrix in cancer prevention. It is anticipated that these resource foods will simultaneously facilitate collaborative research among plant biologists, cancer biologists, and nutrition scientists to evaluate specific foods for their health benefits.

Objectives are:

- Develop plant mutants, transgenics, or other genetically modified food plants with deficient or elevated levels of potential bioactive compounds involved with cancer prevention. Examples might include deletion and over expression mutants for altered starch or antioxidants.
- Evaluate specific bioactive food components or the food matrix as modifiers of cancer risk and tumor prevention.
- Evaluate the food matrix as a modifier of the overall effectiveness of individual bioactive food components.

The proposed initiative will provide new resources to define the physiological role of bioactive components within foods as opposed to isolated components for cancer prevention. The resources will help clarify Inconsistencies among basic, clinical and epidemiological findings about the relationship between diet and cancer. Currently, there is a dearth of NIH awards exploiting plant genomics to test the scientific basis of bioactive compounds in foods as cancer protectants. Consumers are confused about whether food or dietary supplements are the best source of bioactive compounds for health promotion including cancer prevention. The proposed SBIR will assist in providing fundamental information for evaluating the health benefits attributed to specific foods and their components.

Phase I Activities and Expected Deliverables: Phase I will involve development and screening of new plant genetic resources (transgenics, mutants, etc.) with modified levels of bioactive compounds. Development of food resources with both low (deficient) and high (overexpression) levels of bioactive compounds is desired to test model hypotheses and for comparative assessments.

Phase II Activities and Expected Deliverables: Scale-up of plant development and validation of the modified food resources as cancer protectants in either preclinical or clinical studies. It is anticipated that these studies will focus on the ability of these modified foods to modulate genetic pathways involved with cancer processes such as DNA repair, cell proliferation, apoptosis, cell differentiation, carcinogen metabolism, inflammatory response and/or hormone regulation.

205 Metabolomics for Early Cancer Detection

(Fast-Track proposals will be accepted.)

The purpose of this solicitation is to stimulate research to promote the development and improvement of metabolomics technologies for cancer detection. Metabolomics is the study of small molecules, or metabolites present in cells, tissues, and bodily fluids. Representative small molecules include compounds like glucose, cholesterol, ATP,

and lipid signaling molecules. Various cellular responses are associated with the changes in the concentration (flux) or profiles of these small molecules and represent the final events of gene-gene, gene-environment and play a major role in carcinogenesis. When compared to the other biomolecules (DNA, RNA, and proteins), the limited numbers of small molecules make them suitable for analysis by high throughput methods and thus as candidate biomarkers for detection and diagnosis of disease.

Metabolomic approaches are beginning to emerge, but none seems to have the ability to detect early cancers, where the metabolomic changes are minimally affected. In addition, while a number of cancers have been shown to alter metabolite levels in bodily fluids, there is little research on the significance of metabolic changes in association with cancer and the application of metabolomics technologies to early cancer detection or risk assessment.

Phase I Activities and Expected Deliverables: Phase I applications are focused at the development novel technology platforms for cancer detection or improvement of existing technologies for the application of cancer detection with a focus on clinical utility.

Phase II Activities and Expected Deliverables: Phase II proposals will involve the application of the developed technology from Phase I, in a variety of cancer samples to establish the validity of the metabolomic profiling for early cancer detection or risk assessment and evaluate the robustness of the technology that can potentially lead to commercial applications.

206 Methods for Innovative Pharmaceutical Manufacturing and Quality Assurance

(Fast-Track proposals will be accepted.)

Effective use of science and engineering principles during the development of a drug can improve both the efficiency and reliability of the manufacturing process and the quality of the final product. The purpose of this initiative is to facilitate the development of innovative methods that improve and modernize the medical product manufacturing process for biologic drugs for cancer treatment. The focus of this research includes:

1) Development of innovative methods for more rapid and efficient production of biologics by designing, optimizing and monitoring the manufacturing process including new applications of in-line or on-line process analyzers providing multi-variate data to improve the efficiency of process controls and determination of production end-points.

2) Development of formulation design and stability testing strategies that collect information on multiple attributes with minimal sample preparation.

3) Development of methods and reagents to more efficiently assess factors related to the ultimate product quality, safety and efficacy of biologics.

These projects may include but are not limited to development of new or improved manufacturing methods for recombinant protein products, monoclonal antibodies or virus-based therapeutics (herpes simplex, adenovirus or vaccinia) including 1) application of new technologies for monitoring and improving process efficiency 2) development and standardization of new methods to predict and detect safety problems during manufacturing 3) development of tools for product testing including development of *in vitro* assays and new animal models 4) development and production of reference standards and reagents required for GMP manufacturing of a specific product type. The proposed projects must be conducted in compliance with FDA Guidelines for manufacturing biotherapeutics (http://www.fda.gov). The long-term goal of this initiative is to provide the tools necessary for efficient and high-quality manufacturing of novel therapies in the emerging field of cancer biologics.

The FDA recently released a report identifying a gap between the rapid advances in the discovery of potential new therapies and actual medical product development (Challenge and Opportunity on the Critical Path to New Medical Products, FDA, DHHS, March 2004). This report has identified an urgent need for applied research to guide technology development in the production of safe and effective drugs. The potential of recent advances in basic and translational research cannot be fully realized without research targeting the process of creating safe and effective drugs. To address this issue, the FDA has launched a new initiative to encourage development and implementation of innovative approaches to pharmaceutical manufacturing and quality assurance (Guidance for Industry, PAT-A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance, www.FDA.gov).

Significant opportunities exist for improving the efficiency of pharmaceutical manufacturing and quality assurance through the innovative application of novel product and process development controls and modern analytical chemistry. The mission of the Biological Resources Branch of the NCI is to provide resources necessary for evaluation of new therapeutics in a Phase I clinical trial, including drug manufacture (http://web.ncifcrf.gov/research/brb). Consistent with this mission, the NCI seeks to fund projects that focus on the application of novel approaches to the medical product development pathway for cancer therapeutics.

Phase I Activities and Expected Deliverables: Phase I will involve novel inventions related to improvements in manufacturing processes, *in vitro* or *in vivo* assay systems for evaluating the safety and efficacy of a product or class of products, or development of reference standards and reagents required for GMP production of a class of products.

Phase II Activities and Expected Deliverables: Phase II activities will include validation of novel process improvements in manufacturing or production of reference standards, reagents and novel assays systems identified in Phase I. The deliverable for a Phase II project will be a process or product that applies new technology to medical product development.

207 Synthesis Modules for Radiopharmaceutical Production

(Fast-Track proposals will be accepted.)

The purpose of this initiative is to increase the availability and diversity of radiopharmaceutical synthesis modules for research and production activity. There is an increasing and unmet need for synthesis modules that allow for diverse sequences of chemical reactions. This SBIR RFP will encourage small businesses to enter and continue research in development of synthesis modules for radiopharmaceutical production and establish a business producing synthesis modules.

New radioactive compounds (radiopharmaceuticals) are needed to push the frontiers of molecular medicine, both for diagnosis and therapy. In order for new, targeted radiopharmaceuticals to become widespread there must be standardized synthesis procedures that meet GMP requirements. In practice this is usually accomplished by means of synthesis modules that are placed in chemistry hoods with appropriate shielding for radioactivity. These automated, robotic systems ensure that radiopharmaceuticals are synthesized on site to meet QA and regulatory requirements. Synthesis modules make possible the production of the compounds routinely and efficiently, with low personnel radiation dose. Investing in synthesis module research currently for an uncertain market is a high risk activity for small businesses.

Phase I Activities and Expected Deliverables:

- Choice of synthetic method or pathway to pursue; literature search and market research
- Become familiar with FDA regulations governing synthesis modules and the adiopharmaceuticals they produce
- Choice of partner(s) to work with, medical advice and a source of radioactive materials
- Preliminary design for synthesis module based on bench-top methods
- A materials list for the production of synthesis module
- Deliverables: Literature search, design, materials list

Phase II Activities and Expected Deliverables:

- Produce one or more working synthesis modules
- Show production capability and reproducibility with 10 runs
- Analyze the resulting product
- Standard operating procedures for the use of synthesis module
- Demonstration of commercial potential

208 Targetry Systems for Production of Research Radionuclides

(Fast-Track proposals will be accepted.)

The purpose of this initiative is to make available for research (in diagnosis or therapy) radionuclides (radioisotopes) that are either not currently available or not reliably available from any private or public source. Research and development of targetry and production and processing methods are needed to provide a supply of non-standard radionuclides to

investigators at reasonable prices. National laboratories and academic centers have been the traditional sources of research radionuclides. However, it is now increasingly feasible for small businesses to enter and continue research in target production for radionuclides and establish a business producing the targets. This is especially true for cyclotron-produced isotopes, but by forming partnerships with a National Lab or other entity it is also possible for a small business to become involved in the production of reactor-produced isotopes. Examples of radionuclides for which there is a need include, but are not limited to, I-124, Br-76, Cu-64, Y-86, and At-211.

Radioactive elements that are not in commercial production are needed to expand the frontiers of molecular medicine, both for diagnosis and therapy. Each radionuclide (radioisotope) has the chemical signature of its element which permits certain kinds of reactions not available with other elements, and allows the labeling of particular diagnostic or therapeutic drugs. Efficient production of the radionuclides, i.e. production that is not wasteful of expensive bombarding time or expensive enriched target material, requires careful engineering both of the stable target (starting material) and of the handling of the radioactive target after irradiation. Targetry is engineered for the particular circumstances of the irradiating system, both to conform to physical dimensional requirements and to the strength of the irradiating beam.

Phase I Activities and Expected Deliverables:

- Choice of radionuclides to pursue; literature search and survey of current needs
- Choice of partner(s) to work with
- Choice of bombarding system
- Research into starting materials appropriate for available beam energy, bombarding system, and specific activity to be produced
- Plan for investigating target systems and target processing, including a preliminary design
- Materials list for the production of research targets
- Literature search

Phase II Activities and Expected Deliverables:

- Produce one or more working target systems and show production with 10 runs
- Produce standard operating procedures for the targetry system
- Demonstration of commercial potential

215 Methods for the Purification Membrane Proteins and Macromolecular Complexes

(Fast-Track proposals will be accepted.)

The purpose of this initiative is the development and validation of novel methods for the purification of membrane proteins or dynamic macromolecular complexes that are of sufficient purity, high enough concentration, and stable enough for high resolution structural studies.

High resolution structural information of biologically important macromolecules is playing a critical role in understanding complex cellular mechanisms, such as replication, transcription, translation, and protein degradation. This vital information is already being translated into the development of novel therapeutics and new methods for the early detection of cancers. The determination of high resolution structures of soluble individual macromolecules or stable homogeneous macromolecular complexes is becoming routine. However, many of the interactions implicated in the development and growth of cancers take place between insoluble membrane bound factors or in macromolecular complexes that are constantly being remodeled. High resolution structural studies of membrane bound factors and transient macromolecular complexes are difficult to pursue because of the inability to reliably purify these proteins in quantities sufficient for the necessary biophysical experiments. The development of new techniques for obtaining and maintaining membrane bound factors or transient macromolecular complexes in conditions suitable for high resolution biophysical studies is critical to the research communities continuing efforts to understand the mechanisms of cancer.

Phase I Activities and Expected Deliverables: Demonstration of the feasibility of proposed technique.

Phase II Activities and Expected Deliverables: Proof that the technique is applicable in multiple model systems.

Proposals should be focused on the development of novel methods for solubilizing and purifying membrane bound factors or stabilizing and purifying transient macromolecular assemblies in quantities and of a purity sufficient for high resolution structural studies.

216 Development of Inhibitory Reagents for the Study of Protein Function

(Fast-Track proposals will be accepted.)

The purpose of this initiative is to encourage the development and commercialization of new technology for the generation of small molecules and novel mechanisms to modulate protein function within a cancer cell.

The central dogma of biology mandates that, in cellular systems, the ultimate perpetrators of action are proteins. This is true in both normal and transformed cells. While genomic efforts have shed new light on genetic mechanisms and risk factors, aside from the actual identification of genes, they say very little about the ultimate function of the protein products. Even predictions made from genetic sequences can only tell part of the answer. One of the most powerful ways, currently, to infer a gene's function has been to alter its expression, commonly through the painstaking construction of genetically modified model organism. Transgenic and "knock-out" animals have proved invaluable in the understanding of gene function. Despite the success of these approaches, they remain hampered by the constraints outlined above. This is compounded by such cellular events as transcription/ translation control, alternate splicing, and protein turnover, which further remove the effector protein from its genetic origin. Recently, increased efforts have been underway to develop sophisticated approaches for specific control at the level of the transcript or the actual protein. Many of these approaches use interfering RNA or specific protein inhibitors. When fully realized these approaches allow a much more specific and quantitative control over a protein's function. These approaches should prove a valuable complement to genetic approaches helping to understand biological behavior of specific proteins. This type of knowledge is critical for the greater understanding of the transformation process. Products generated out of this program would have a broad impact on many of the current NCI Strategic Priorities including, molecular epidemiology and the identification of biomarkers, integrative cancer biology, cancer interventions, and early detection.

Phase I Activities and expected deliverables:
The applicant should develop or improve a technology capable of specifically modulating the expression or functionality of a protein. The Phase one will focus on the reagent/approach development and feasibility testing. The approach should be compatible with various cellular and/or model systems. Delivery systems, while not an essential component of the system, should also be considered. Developed systems should also incorporate the appropriate monitoring of RNA/protein level.

Phase II Activities and expected deliverables:
Expanding on the Phase I goals, the contractor should expand the developed system or reagent into a specific cancer cell, showing impact across a wide range of functional and physiological parameters. Expansion into this phase will also encourage the PI to expand into multiple cells and potential in vivo studies.

217 Nanoparticle Biosensors for Recognition of Exposure and Risk Analysis in Cancer

(Fast-Track proposals will be accepted.)

The purpose of this initiative is to develop nanoparticle-based sensors with improved sensitivity and specificity for a) early detection and post-treatment monitoring of cancer signatures using genomic and proteomic means operating in both in-vitro and in-vivo environments.

Multifunctional nanoparticles provide for an attractive alternative towards designing novel sensor platforms for recognition of genomic and proteomic signatures in cancer. The use of nano-object labels: quantum dots, nano-rods, and nano-wires permits for highly multiplex tagging of unknown molecules in a sample and their subsequent tag-by-tag recognition. These recognition can be carried our using optical or electrochemical means. Gold nanoparticles have been used for enhanced sensitivity recognition of DNA duplexes.

With diversified availability of nanoparticles in quantum dot, denrimer, and liposome families, in vivo sensors which target preferentially cancer cells within the body can be also envisaged. The reporting of recognition event can be achieved through various imaging methods or possibly through transmitting data to an external data capture system.

The short term goal (18 months) of this program is to demonstrate an *in-vitro* nanoparticle-based sensor

platform. Nanoparticles should be used as: 1) analyte labels, or 2) act as direct sensor/signal transducers in individual or distributed (nanophase film) manner.

The attributes of the solution should be the following:

- capability to detect both DNA and protein signatures
  - at least 10-plex detection capability (recognition of 10 independent signatures, simultaneously)
  - detection platform should be 'optics-free' and rely on electronic, magnetic, or other non-optical means of recognition.

The long term goal (36 months) of this program is:

- scale-up *in-vitro* sensor to 50 signatures
- provide ability of detecting signatures from 'real' samples (bodily fluids)
- introduce particle solutions to *in-vivo* sensing platform. Particle size should be small enough to provide for vasculature and cellular membrane penetration. This particle needs to carry a recognition (sensing) payload enabling specific binding to cancer cells. In addition the quantitative reporter of the binding event needs to be facilitated. This could be accomplished through optical, magnetic imaging or data transmission to external data hub.

The development of sensitive and specific sensors is crucial for early recognition of cancer and the monitoring of post-treatment behavior.

Phase I Activities and expected deliverables:

- Design describing:
  - sensing and transduction methodology
  - particles selected for the solution (their commercial source or synthesis method) and
  - expected recognition sensitivities
  - expected false positive rate
- Provide proof of concept demonstration using purified sample

Phase II Activities and expected deliverables:

- Provide a working prototype of in-vitro sensor system
- Demonstrate sensor sensitivity and specificity for 'real' samples. Compare with results from Phase I.
- Demonstrate proof-of-concept in-vivo sensing solution in cell culture environment

218 Development of Novel Methylation Assays for Cancer Detection

(Fast-Track proposals will be accepted.)

The purpose of this initiative is to encourage development of innovative methods that do not require bisulfite treatment to quantitatively measure CpG methylation of specific genes, development of methods that substantially increase the conversion rate of cytosines to uracils by bisulfite, for cancer early detection and development of methylation detection kits for commercialization.

Recent advances in epigenetics, especially in DNA methylation, provide great promise for noninvasive methods for early detection of cancerous lesions. However, there is no single methylation marker or panel of methylation markers that has sufficient sensitivity and specificity to accurately and reliably detect early cancers. Furthermore, technology and methods for methylation detection need to be improved to increase specificity and sensitivity as well as throughput. Most methods to measure CpG methylation at specific sites require bisulite treatment, which is time consuming, and the incomplete conversion of cytosines to uracils can cause fluctuations in methylation measurements. Through the SBIR contract mechanism, methods will be developed to improve the use of DNA methylation for early cancer detection and prediction.

Phase I Activities and Expected Deliverables:
1) Develop innovative methods that do not require bisulfite treatment or that substantially increase the conversion rate of cytosines to uracils by bisulfite to quantitatively measure CpG methylation of 5 to 10 genes, which will be recommended by the Early Detection Research Network (EDRN) or academic investigators; 2) Test the usefulness of these methods using DNA extracted from cell lines or clinical samples, which have been recommended by the EDRN or academic investigators.

Phase II Activities and Expected Deliverables:
1) Cross validation of the developed methylation

methods to test accuracy and reproducibility; 2) Use these methods to test the methylation status for 30 genes; 3) Validate the methods using clinical samples. This will be done in collaboration with EDRN investigators and academic investigators; 4) Plan for commercializing methylation detection kits using these methods.

219 Platform Biosensor Technologies for Point-of-Care Cancer Diagnostics

(Fast-Track proposals will be accepted.)

The long term goal of this proposal is to facilitate the development and application of novel multi-channel point of care (POC) platform biosensor technology for cancer diagnostics. Biosensors are devices that combine a biochemical recognition/binding element (ligand) with a signal conversion unit (transducer); point of care testing is diagnostic testing that is performed on site, providing results that may impact patient care almost immediately.

The short term goal of this initiative is to develop a computer controlled platform of automatic, user-friendly, stand-alone POC devices for analysis of 20 or more DNA/RNA or protein targets in clinical samples simultaneously. The devices must be capable of carrying out rapid assays (less than two hours) at modest cost (less than $5 for a sample for all targets and a total cost of the instrument, less than $2,000 excluding the computer cost when 1000 units produced) and should not include biohazard materials. Preference will be given to open platform technologies.

The device should contain two modules

1. Two disposable assay modules one for nucleic acid-based and one for protein-based analysis compatible with the detector (phase I). The assay modules should be flexible to allow adaptation for new assay strategies (for example, a new epigenetic analysis).
2. A detector that incorporate the disposable assay modules and includes transducer, fluidic system and the operator interface, based on any existing transducer technology (phase II).

Protein Analysis: The device must be capable of automatically detecting and analyzing proteins at concentrations of 1 ng/ml or less in serum, using immunological or other detection systems. The device must be compatible with tissue protein sample preparation methods and have specificity and sensitivity comparable or better than current ELISA technology. For phase I, the measurements can be done using any conventional method.

Nucleic acid analysis: The device must amplify DNA/RNA from clinical samples more than 10^5-fold (or directly detect 0.005 attomoles, ~ 3000 target molecules) and detect and analyze the amplicon (or sample) automatically. The analysis may include detection of SNPs, genomic rearrangements, epigenetic changes and transcription patterns. The device must be compatible with current clinical tissue DNA/RNA sample preparation methods. The specificity and the sensitivity must be comparable to current nucleic acid analysis technologies. For phase I, the measurements can be done using any conventional method.

POC diagnostics may reduce costs, and expand the availability of testing especially in traditionally underserved populations to overcome health disparities.

Phase I Activities and expected deliverables: Development of disposable assay modules and proof of principle.

1. Preliminary design POC disposable assay modules (for DNA/RNA and proteins) using bench-top methods (including chemistries for ligands attachment).
2. Provide four working prototypes, two for each of the two disposable assay modules.
3. Testing of the assay modules with purified analytes and with purified analytes spiked in serum using any conventional detection method.
4. Defining sensitivity, selectivity and the device fail rate using a total of 500 replicas for the four types of tests (purified and spiked analytes of DNA/RNA and proteins) using statistical analysis of the data.
5. Conducting a cost analysis based on production of 1000 assay modules
6. Evaluation of potential for commercial applications.

Phase II Activities and expected deliverables: Development of the detector, evaluation of the device in research or clinical setting for the robustness and sensitivity using selected target molecules in clinical samples.

1. Develop a detector module for the assay modules based on bench-top methods

2. Define a statistically justified sample size to establish sensitivity and selectivity of the integrated device (detector and assay modules).
3. Test the integrated device with purified analytes (DNA/RNA and protein) and with the purified analytes spiked in serum (or other clinical samples) with a sample size defined in phase II steps 2 but no less than 200 replicas with each module for each sample types (purified and clinical).
4. Define sensitivity, selectivity and fail rate of the device for purified analytes in spiked clinical samples for each of the four test types in phase II step 3 in research or clinical setting.
5. Develop and provide a prototype (integration of the detector and assay modules to a stand alone instrument controlled by a laptop computer).

220 Chemical Optimization and Structure-Activity Relationships

(Fast-Track proposals will be accepted.)

The goal of this initiative is clinical development candidate identification through synthesis, analog development and structure-activity relationship studies of screening leads.

High throughput screening campaigns of more than 140,000 samples from the NCI repository addressing a number of molecular targets of potential therapeutic significance in cancer routinely identify lead compounds with potent and selective activity (http://dtp.nci.nih.gov/). While preliminary structure-activity studies can sometimes be performed with available analogs in the repository, much additional work is needed to optimize the screening leads for potency and pharmaceutical properties (bioavailability, pharmacokinetics, metabolism, formulation) consistent with clinical development. Current target compounds of interest include hits from four of our antitumor molecular targeted screens; the chemical structures represented are quite diverse, but amenable to synthesis and analoging.

The Screening Technologies Branch of the Developmental Therapeutics Program has attempted to develop and will continue to pursue Cooperative Research and Development Agreement (CRADA) partnerships for this need, but efforts to date indicate that the companies most capable of and disposed toward conducting this type of research are small, frequently startup, entities with minimal to no resources to commit to such a project, despite their intrinsic interest and expertise. The SBIR mechanism would provide the initial seed funds to move such a project from concept (screening lead) to something with considerably more commercial potential (preclinical development candidate).

Phase I Activities and Expected Deliverables:
The lead compound will be synthesized, if necessary, to provide sufficient material for secondary testing and preliminary in vivo evaluation. At the same time, a limited series of analogs will be prepared, with the goal of defining the critical structural elements necessary for activity. The net result of Phase I research should be a confirmed lead compound with good potency and pharmaceutical properties.

Phase II Activities and Expected Deliverables:
Additional synthetic work will be undertaken to refine the previously identified lead structure, with the goal of maximizing potency and other desirable attributes while minimizing toxicity and other undesirable attributes. Here, a larger series of more closely related analogs would likely be prepared and evaluated in primary and, as appropriate, secondary screens. Sufficient quantities of the lead compound(s) will be necessary for detailed pharmacological evaluation. The net result of Phase II research should be identification of a clinical development candidate. Some areas likely to be covered in successful proposals include:

a) Analog synthesis/medicinal chemistry
b) Structure-activity relationships
c) Efficient synthesis of selected lead compound(s)
d) Scale up synthesis of clinical development candidate
e) ADME (absorption, distribution, metabolism) and formulation studies

Disclosure of Lead Compounds – Confidentiality Agreement

In order to provide a comprehensive review of the capabilities of offerors, interested parties shall be required to submit a synthesis plan (to provide sufficient material for secondary testing and preliminary in vivo evaluation) and an analog plan (with the goal of defining the critical structure

elements necessary for activity) for a compound/drug of interest to the NCI.

The compounds assigned for clinical development are often those procured by the NCI under the terms of confidentiality agreements. Since the compound/drug will be provided by the NCI, interested parties shall be required to **execute a confidentiality agreement** prior to being provided with the compound/drug. To obtain a confidentiality agreement for this Topic only, please send an e-mail to the Contracting Officer (CO) at mg354x@nih.gov. Once an offeror has an executed confidentiality agreement in place, information regarding the compound/drug of interest shall be provided for the offeror's use in preparing a response to this SBIR Topic.

In order to obtain the compound/drug of interest to the NCI, interest parties shall execute a confidentiality agreement (between the offeror and the NCI) within forty calendar days of the 'issue date' of this solicitation. No requests for compound/drug shall be accepted after this deadline.

221 Oral Bioavailability Enhancement of Drug Candidates Using Innovative Excipients

(Fast-Track proposals will be accepted.)

Lack of sufficient oral bioavailability of potential drug candidates hinders development to their full potential. By enhancing the oral bioavailability of such compounds, therapeutically beneficial products could be developed, especially where long term exposure is needed for maximum therapeutic effect. DTP has a number of drug candidates for use as test cases as well as development into viable clinical candidates.

If successful, these techniques can be applied to a number of existing drugs as well as to several potential drug candidates in the Developmental Therapeutics Program (DTP) pipeline. It is our plan to apply successful formulation strategies to reduce or eliminate the need for protracted intravenous delivery of drugs. This will not only benefit patients in terms of convenience, but also will reduce the overall costs of evaluation/treatment by reducing or eliminating hospitalization and/or visits to clinics

Currently many of the chemotherapeutic agents are administered as intravenous infusions, sometimes for long period of time. For example, CDDO, a new drug entering into NCI clinical trials need to be continuously infused for five days, with further plans to increase the duration to ten days and beyond. The iv formulation of the 17-AAG, a geldanamycin derivative currently undergoing extensive Phase II evaluation, contains DMSO and lecithin and requires special aseptic processing, limiting its scale up. Betulinic Acid, potential clinical candidate that came through the RAID mechanism, was abandoned because of lack of oral bioavailability. It was meant for a chronic dosing and no viable, non-toxic, iv formulation could be developed. All these drugs and several others, either already in the clinic, or progressing through DTP preclinical evaluations could benefit from enhanced bioavailability.

Capsules and tablets are most preferred dosage forms for chronic use of medicaments and should be the case for cytostatic and chemo-preventive drugs if the enhanced bioavailability oral products for these categories are available. DTP and NCI will benefit by using either special chemical enhancers or drug delivery systems to increase oral bioavailability of the compounds of interest.

Phase I Activities and Expected Deliverables:
After identifying the compounds suitable for the selected technology, some prototype formulations will be developed and various parameters will be examined by evaluating the oral bioavailability of the active ingredient in animal models. These parameters will then be used to optimize the final dosage form and evaluate its shelf stability under accelerated conditions.

Phase II Activities and Expected Deliverables:
The product will be scaled up to produce batches, under GMP conditions, for dose range finding studies and long term GLP toxicological evaluation. Upon favorable results, it is likely that these formulations will be evaluated in human clinical trials by the NCI.

222 Investigation of the Production Parameters of Microbial Natural Products

(Fast-Track proposals will be accepted.)

The goal of this initiative is the derivation of fermentation production parameters of materials of interest to the Developmental Therapeutics Program and the Center for Cancer Research as both probes of biological systems related to cancer chemotherapies and of potential usage as intermediates in chemical modification in order to develop new therapeutic modalities. NCI would provide organisms, standards and initial analytical information.

The long-term goal is proof that the parameters obtained will function in larger-scale fermentations (up to 250 L operating volume) and investigation of the potential for semi-continuous fermentative production.

A significant number of microbial natural products (e.g., leptomycins, wortmannin, pleurotin, fumitremorgins) have evinced significant interest in recent years by researchers associated with DTP and CCR as both probes of mechanisms related to cellular metabolism in cancer, and as potential sources of starting materials for chemical derivatization in order to alter the PK/PD characteristics of other analogues en route to clinical trials.

Although these materials have been produced on a small scale (usually utilizing multiple shake flask or 2-10L fermentations), nothing has been published on the parameters necessary for their production on larger scales in any optimized format. Thus any request for these agents from within NCI (and / or collaborators) is extremely difficult to fill as the necessary biochemical engineering data are not available in the open literature nor from any of the small scale work done by DTP-related contractors at NCI-Frederick.

As examples of the interest that two of these agents have recently evoked, there is currently a request under the RAID Program for 100 grams of wortmannin as a starting agent for chemical modification, and the potential for leptomycins (or derivatives) as components of treatment regimens that may overcome the resistance mechanisms shown by Gleevec® and potentially other agents with similar initial mechanisms by stopping nuclear transport by the inhibition of *crm*1, leading to apoptosis.

Phase I Activities and Expected Deliverables:
The first phase would be the derivation of optimized conditions for production on up to 50 L operating volume with organisms and initial information provided by NPB/DTP. The deliverables would be a report with the fermentation parameters, in particular the volumetric production rates and yield to purification for fermentative production of specific compounds.

Phase II Activities and Expected Deliverables:
The further optimization of production of selected agents on a scale up to 250 L operating volume with investigation of the potential for semi-continuous fermentative production of a selected agent. The initial deliverables would be similar to those in Phase I, but would be extended to include delivery of purified product(s) on a scale to be determined in conjunction with the project officer.

223 Synthesis and High-throughput Screening of in vivo Cancer Molecular Imaging Agent

(Fast-Track proposals will be accepted.)

The purpose of this contract is 1) to develop robust synthetic methodologies for the generation of complex libraries of in vivo cancer imaging agents with direct clinical potential, and 2) to demonstrate the utility of the resulting libraries in a high-throughput screen using a cancer-specific assay.

The synthetic methodologies for the generation of complex libraries of molecules for high-throughput screening for cancer drug discovery and development have been advancing rapidly. In contrast, the development of methodologies for the generation of complex libraries of targeted, clinically-relevant, in vivo cancer molecular imaging agents, and for the high-throughput screening of those libraries are far less advanced. The design and synthesis of targeted, in vivo cancer imaging agents such as small molecules, peptides or other bio-compatible substrates, must take into account at least two major considerations. First, a functional domain of the imaging agent must be capable of specifically recognizing a cancer target. Second, the chemical moieties necessary for eventual in vivo detection must be stably integrated into the agent in a manner that does not adversely affect the targeting capability of the functional domain. Following the generation of these complex molecules, assays appropriate for high-throughput screening must be developed or modified from existing assays. This contract solicits proposals to support the advancement of this field through the following activities:

Phase I Activities and Expected Deliverables:

- Development of a methodology for the synthesis of a library of bio-compatible molecules with clinical applications that integrate both a cancer-targeting domain and a detection domain.
- Generation of a small-scale pilot library of in vivo cancer molecular imaging agents using the developed synthetic methodologies as a proof-of-principle.
- Feasibility testing of the pilot library in a cancer-specific, high-throughput assay

Phase II Activities and Expected Deliverables:

- Generation of one or more large-scale libraries of in vivo cancer molecular imaging agents
- High-throughput screening of the resulting libraries for an in vivo cancer molecular imaging agents that will be commercialized as a clinical cancer imaging agent.

NIH is aware that not all SBIR medical and behavioral research projects can be completed within the statutory guidelines, i.e., $100,000 and six months for Phase I and $750,000 and two years for Phase II. Therefore, applicants are encouraged to propose a reasonable, appropriate, and justified budget and project period necessary to complete the Phase I or Phase II research project. Deviations from the statutory guidelines MUST be well justified.

224 Developing Diagnostically Aided Active Targeted Delivery Systems for Chemotherapeutic Agents

(Fast-Track proposals will be accepted.)

The goal of this initiative is targeted delivery of anticancer agents provides enhanced tumor uptake eliminating or reducing systemic side effects. Such techniques are also useful to target drugs to stay away from certain organs in which they produce toxic effects. Use of such delivery systems will enable DTP to develop very active chemicals, otherwise impossible to develop due to their potent side effects, into clinically useful drugs. Examples of useful delivery systems include quantum dots, multifunctional liposomes and multi variable dendrimers, either individually or in different combinations. Tumor selectivity may be achieved with antibodies, transferrin or folic acid.

Once identified, the targeted delivery techniques will be applied to DTP drug candidates and to evaluate targeting potential in preclinical animal models. These evaluations can be achieved in tumor bearing animals by non invasive techniques such as fluorescence imaging (in case of functionalized Quantum Dots), inclusion of radionuclides or contrast agents (in case of liposomes or dendrimers). This information will be used to develop elegant and highly targeted drug products to achieve selectivity and specificity. With development of **non-toxic** delivery platforms, we envision application of these techniques to deliver potent drugs to patients to achieve great therapeutic benefit with little or no toxicity.

Currently, many cytotoxic drugs are not developed or fail in the clinic because of lack of reasonable therapeutic index (TI). A recent example of a drug candidate in our pipeline is Breflate (a Brefeldin A prodrug), which could not be developed due to neuro-toxicity at doses that were very effective in preclinical animal models. If this molecule could be targeted to the tumor and away from the CNS, it would have been a very useful drug. Most of the drugs with narrow therapeutic window (less potent and highly toxic side effects) could benefit from such targeted delivery platforms. Use of platforms to be developed under this effort will allow us to direct drugs of interest to the desired sites and allow us to "visualize" their distribution by non invasive techniques. Once optimized, these techniques have a great potential for human applications.

Phase I Activities and Expected Deliverables:
After identifying the compounds suitable for selected delivery technology, some prototype formulations will be prepared and evaluated in tumor bearing animal models for targeting and "visualization." These results will then be used to optimize and further refinement.

Phase II Activities and Expected Deliverables:
In this phase the product(s) will be scaled up for efficacy studies, dose range finding studies and possible GLP toxicological evaluation. If successful, a few drug candidates may be evaluated in a Phase 0 clinical trial setting.

225 Home Centered Coordinated Cancer Care System

(Fast-Track proposals will not be accepted.)

The Veterans Health Administration, with its enterprise wide computerized patient record, telehealth technologies and coordinated care model, offers a working prototype of a home based system of coordinated care for chronic conditions. The VHA, in partnership with NCI, has developed a system of coordinated cancer care made up of these components. This system has shown promise for the effective management of symptoms and high quality of life during cancer treatment. It has the additional potential of saving costs due to unnecessary institutionalization. The health information infrastructure that supports this system requires a high level of interoperability as does the human communication processes that make the coordination among the team seamless and dependable. The VA/NCI cancer care coordination processes are similar to disease management

processes. They are led by a professional care coordinator who brings community resources to bear upon the various symptoms as they are experienced by the patient. The care coordinator is responsible for monitoring the patients' symptoms on a daily basis and providing feedback regarding appropriate self or professional symptom management actions given the patient's current status. The patient and/or informal caregiver are responsible for answering daily questions and implementing self care symptom management. Daily patient/provider dialogue is supported by a telehealth program that is linked to the VA's computerized health record.

The goal of this project is to develop an automated coordination tracking program that will allow all cancer care team members a view of the VA/NCI cancer care coordination processes. An automated cancer care coordination tracking program will track health status and outcomes data, symptom management recommendations, interventions and decision points in real time and in full view of all team members. It will register handshakes (responsibility hand-offs) and all feedback loops throughout the coordination of a given activity. Ideally this software should include a real time visual simulation of the coordination process with alerts, reminders and other signals that support the accountability of individual team members and the integrity of the entire coordination effort. This program is not to be a stand alone product but should be integrated into a larger system of home based coordinated cancer care.

In early 2003 the NCI announced its goal of "eliminating the suffering and death due to cancer by 2015." There is an expected total of 1,358,030 new cancer cases in the US in 2005 (Jemal, Murray, & Ward, 2005). Among 19 million outpatient visits made by cancer patients each year, chemotherapy is administered in approximately 22% of those visits (Hewitt & Simone, 1999). Cancer chemotherapy successfully treats many cancer cells, but causes severe symptoms, such as fatigue, pain, and nausea (Mooney, Beck, & Friedman, 2002). Uncontrolled symptoms, many of which can be profound and are primarily experienced by patients at home, are associated with a reduction in health-related quality of life (HRQL) (Cooley, Short, & Moriarty, 2003; Mooney et al., 2002). A recent study of 117 lung cancer patients found that many symptoms (e.g., pain and fatigue) decreased from 0 to 3 months, but from 3 to 6 months pain and fatigue increased markedly (Cooley et al., 2003). Patients' quality of life is too often compromised as a result of either the cancer and/or its treatment (Hammerlid, Silander, & Hornestam, 2001). The current standard of practice for managing symptoms during chemotherapy is for a health provider to address them when the patient comes in to the hospital or clinic for treatments, sometimes days or weeks apart (NIH, 2002).

In an effort to reduce suffering due to cancer and its treatment's side effects in a more effectively manner, the Health Communication and Informatics Research Branch in the Division of Cancer Control and Population Studies at NCI has partnered with the Veterans Health Administration (VHA) to develop and test a model of coordinated cancer care. We have designed, implemented, and tested a working model based upon a systems view of human communication and informatics and upon the VA's Community Care Coordination Service model (Harris, L; Kobb, R; Ryan, P; Darkins, A; Kreps, G. "Research as Dialogue: Health Communication and Behavior Change in Patients' Natural Habitat" in Whitten, P and Cook, D (Eds) *Understanding Health Communication Technologies.* San Francisco, Jossey Bass. Pp91-100; Chumbler, N; Richardson, L; Harris, L, et al. "Cancer Care Dialogues: Empirical Support for Complex Adaptive Systems Research and Practice" in Whitten, P., Kreps, G.L., & Eastin, M. (Eds.). (2006, In press). *Advances in Cancer Online Information Services.* Cresskill, NJ: Hampton Press; Meyer, M; Kobb, R; and Ryan, P. "Virtually Healthy: Chronic Disease Management in the Home" *Disease Management,* Vol 5, No.2, 2002, pp87-94.

The VA/NCI home centered coordinated cancer care system holds promise for the thousands of Veterans who have cancer. We expect this project to standardize and extend this model to others outside the VA.

Phase I Activities and Expected Deliverables:

- Offerer must work with one of the communities recommended by the Foundation for eHealth Initiative. Contact information may be found on their website (www.ehealthinitiative.org). The Foundation for eHealth Initiative provides seed funding and support to multi-stakeholder collaboratives within communities (both geographic and non-geographic) who are using electronic health information exchanges (HIE) and other information technology tools to drive improvements in healthcare quality, safety, and efficiency;
- Community members must be included on the research and development team during all Phase I activities;

- Review the VA/NCI cancer care coordination model, other coordination protocols and relevant literature to develop an overall cancer coordination process model;
- Establish a team or set of teams that will conduct cancer care coordination, including their roles and responsibilities;
- Conduct interviews with team members and selected community participants to develop a set of use case scenarios (from diagnosis through survivorship/death for one cancer type) that will serve as the basis of the coordination simulation software program;
- Provide a report detailing the coordination tracking program design, including a theoretical and methodological bases for the evaluation;
- Provide a set of use case scenarios that have been approved by members of the team for tracking;
- Develop a prototype of the cancer care coordination tracking program;
- Obtain letters of agreements from appropriate community participants to participate in the testing and evaluation of the cancer coordination system in the Phase II;
- Present Phase I findings to an NCI Evaluation Panel.

Phase II Activities and Expected Deliverables:

- Offerer must continue their development work with one of the communities recommended by the Foundation for eHealth Initiative. Contact information may be found on their website (www.ehealthinitiative.org);
- Community members must be included on the research and development team during all Phase II activities;
- Complete 2 iterations of the tracking program software, including technical documentation of the system and a training manual;
- Develop evaluation measures;
- Evaluate and refine the program based upon user feedback;
- Integrate the tracking program into a telehealth monitoring and computerized patient record;
- Test and evaluate the complete system serving cancer patients and their care coordination team using process and outcome measures as described above;

System Requirements include:

  - Embedding the tracking software into a home telehealth monitoring and reporting system based upon the VA/NCI model of home centered coordinated cancer care; this could involve partnering or licensing with other vendors or developers of these components.
  - Integrating the home centered coordinated cancer care system into a community's existing IT infrastructure using the IT interoperability standards offered by The U.S. Department of Health and Human Services (www.hhs.gov/healthit).

- Publish at least one article describing the development and evaluation of the system;
- Present Phase II findings to an NCI Evaluation Panel;
- Present at a Product Showcase sponsored by DCCPS, NCI.

226 A Clinical Decision Support Tool to Promote Evidence-Based Screening and Intervention with Tobacco Users

(Fast-Track proposals will not be accepted.)

The goal of this initiative is, using a user-centered approach, design and produce a clinical decision support tool to help health care providers screen and intervene appropriately with their patients who use tobacco while simultaneously tracking provider adherence to evidence based clinical practice guidelines. A Personal Digital Assistant (PDA)-based platform with web-based distribution is sought for this purpose. This tool, as conceived, or others must be applicable in Cancer Centers and other settings where NCI Investigators conduct clinical care.

The National Cancer Institute has set a goal to eliminate suffering and death due to cancer by the year 2015. One-third of all cancers are tobacco related and approximately 90% of lung cancers are attributable to tobacco. Therefore, it is essential that we shore up our efforts in tobacco control if we are to meet this goal.

Only 59% of health care providers advise their patients to quit tobacco use. The number of providers who provide assistance with quitting is

even lower. Surveys of nurses show that only 3-6% follow the Public Health Service's clinical practice guideline: Treating Tobacco Use and Dependence. NCI seeks proposals from vendors to develop tools to ensure that health care providers are following all steps outlined in the evidence based guidelines; that is, that providers are not only assessing and advising patients to quit, but are actively assisting them in doing so. The use of PDAs by physicians has increased from 26% in 2001 to 57% in 2005 and the use of PDAs to facilitate adherence to clinical practice guidelines has been advocated. Therefore, NCI is especially interested in proposals that focus on developing PDA-based tools. A key feature of the tool is to track, monitor, and study provider behavior vis-à-vis the practice guidelines. Proposals should describe how the system would implement appropriate security to insure compliance with federal mandates for patient data privacy. Proposals should also describe features to track and monitor provider behavior.

Phase I Activities and Expected Deliverables:

- Develop the content for a set of core instruments and product features, including those that would electronically track and monitor provider behavior.
- Produce an initial product prototype.
- Conduct usability testing with the product prototype with representative users (e.g., health care providers in NCI research settings and Cancer Centers).
- Make modifications to the prototype based on the results of usability testing.
- Conduct a field test/feasibility study with health care providers in NCI research settings and Cancer Centers.
- Establish prototype revisions/additions to be implemented and tested in Phase II.
- Present Phase I findings to an NCI Evaluation Panel.

Phase II Activities and Expected Deliverables:

- Implementation strategy and project plan for a fully functional clinical decision support tool.
- Full working software that implements the user-centered features, functions and requirements developed in Phase I.
- Technical documentation of the tool, including software code, programming interfaces, and hardware requirements.
- A large scale study or clinical trial demonstrating the tool's efficacy in getting providers to deliver evidence based treatment to their patients who use tobacco and also demonstrating the tool's ability to accurately capture data on provider behavior. Data security should also be demonstrated. Study participants should be 100-200 health care providers, including NCI investigators, from a variety of subspecialties, and working in diverse settings.
- Publish at least one article describing the development and evaluation of the system.
- Presentation of Phase II findings to an NCI Evaluation Panel.
- Presentation in a Product Showcase sponsored by DCCPS, NCI.

227 Quantum Dot Nanotechnology to Detect Oncogenic Human Papillomaviruses

(Fast-Track proposals will not be accepted.)

The goal of this initiative is to develop a kit enabling quantitative detection of human papillomavirus DNA and related markers in liquid-based cervical cytology specimens.

Although cytologic screening has markedly reduced cervical cancer incidence and mortality, cytologic testing is poorly reproducible and lacks single-test sensitivity. Accordingly, iterative screening and intensive follow-up are required to achieve maximal cancer prevention. Patients with abnormal cytologic screening tests are referred for colposcopy and biopsy to achieve definitive diagnosis; however, colposcopy often yields erroneous assessments and biopsies are often misplaced. Approximately 13 oncogenic human papillomavirus (HPV) types represent the necessary causal agents of nearly every cervical cancer. Assays for detecting HPV DNA in cellular extracts have demonstrated clinical utility; however, none of these tests can accurately predict the fate of an HPV infection, which remains a critical requirement given that the cumulative lifetime prevalence of infection exceeds 50% and that the vast majority of these infections spontaneously regress. The development of molecular bar coding using quantum dot labeled beads may permit more predictive multi-parameter molecular testing by allowing simultaneous assessment of morphology,

HPV DNA detection, and evaluation of parameters such as: proliferation and expression of HPV E6 and E7, p16, and 3q amplification. Using quantum dot technology (Q Dots) with multiple photostable nanocrystals possessing appropriate excitation and emission spectra, it may possible to develop a sensitive assay for simultaneously detecting multiple markers related to HPV infections. This would require development of Q Dots suitable for detecting DNA, RNA, and protein targets. Guide to NCI's Nanotechnology initiative http://otir.nci.nih.gov/brochure.pdf.

Phase I Activities and expected deliverables:
The successful respondent will provide proof-of-concept by developing an assay for detecting common oncogenic HPV infections (types 16, 18, and possibly others) and concurrently assessing proliferation, HPV E6 and E7 mRNA, p16, and 3q amplification (or comparable markers) in liquid-based cervical cytology specimens and tissues (frozen and fixed). The respondent will provide equipment and reagents; NCI will help with sample collection. The respondent will establish the sensitivity and reproducibility of the method by comparing results of Q Dot assays to those of other techniques. Using tissues, the respondent should assess the depth and kinetics of absorption and penetration of quantum dot reagents and characterize the properties of emitted fluorescence.

Phase II Activities and expected deliverables:
The successful respondent will produce kits suitable for clinical testing of liquid-based cytology specimens, including protocols for assay performance and interpretation. The kits shall demonstrate reliable performance characteristics when stored under conditions and for time intervals similar to those required for comparable pathology reagents. If methods for producing non-toxic Q Dot reagents become available during the contract period, the respondent will work with NCI during that period to develop a test permitting visualization of cervical lesions *in vivo*; this method could potentially replace examination of magnified images of the cervix following application of iodine or acetic acid (colposcopy).

228 Quantum Dot Nanotechnology to Quantify Marker Expression in Breast Cancer

(Fast-Track proposals will not be accepted.)

The goal of this initiative is to develop a kit for quantitatively measuring co-expressed markers in breast cancer

Assessing expression of estrogen receptor alpha (ER) and progesterone receptor (PR) in breast cancer is useful for understanding etiology, predicting responses to hormonal treatments (e.g. tamoxifen), and establishing prognoses. Although immunostains for ER, PR, Her2/neu, and proliferation markers are routinely performed for clinical management, performance and interpretation of these assays have not been standardized, provide limited quantitative data, and inconsistently predict treatment responses (e.g. 50 to 60% of ER-positive cancers fail to respond to hormonal therapy, whereas 5 to 10% of ER-negative cancers do). Increasing use of aromatase inhibitors has created a similar need for optimized assays. Quantum dot (QDot) nanotechnology is a promising method for meeting this requirement.

Using reagent antibodies linked to QDots with photo-stable, discrete non-overlapping emission spectra could permit the development of a clinical test with optimal sensitivity and quantitative labeling capability that would permit simultaneous measurement of several markers within cells in small specimens. Co-expression of markers may define unique phenotypes (e.g. cancers triply negative for ER / PR / Her2/neu may be biologically aggressive; cancers positive for both ER and Her2/neu may predict poor response to tamoxifen). Double labeling assays are challenging to perform using conventional techniques. Finally, use of QDOTs to stain gross unfixed specimens may permit topographic mapping of marker levels on a macroscopic scale, allowing detection of tumor sub-populations with differing aggressiveness or treatment responses.

Guide to NCI's Nanotechnology initiative http://otir.nci.nih.gov/brochure.pdf.

Phase I Activities and expected deliverables:
The successful respondent will provide proof-of-concept that it is possible to measure ER, PR, Her2/neu, proliferation, and aromatase (or comparable targets) simultaneously in both frozen and fixed (buffered formalin) breast tumor tissue. Results of QDot assays will be compared to "gold standard" assays (e.g. Western blots, biochemical assays, etc.). Phase I will demonstrate the feasibility of relating QDot data to objective standards such as number of receptors / cell, S-phase percentage, percentage of cells with Her2/neu amplification, etc. The respondent will assess the feasibility of developing a QDot system for assessing distribution and intensity of selected marker expression in gross unfixed tissues (human or animal specimens). The respondent will supply equipment and reagents

required, including nanocrystals, and develop detection methods that meet performance standards. The National Cancer Institute will provide limited assistance to the respondent in obtaining tumor tissues for use in assay development and in reviewing pathology specimens, as necessary.

Phase II Activities and expected deliverables: The respondent will produce kits for microscopic (and potentially macroscopic) testing for multiple breast markers simultaneously; instructions for interpretation; and data relating the QDot assay results to objective metrics. The kits shall demonstrate reliable performance characteristics when stored under conditions and for time intervals similar to those required for comparable pathology reagents.

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

NIDA's mission is to lead the nation in bringing the power of science to bear on drug abuse and addiction, through support and conduct of research across a broad range of disciplines and by ensuring rapid and effective dissemination and use of research results to improve prevention, treatment, and policy.

This solicitation invites proposals in the following areas:

064 Nanoscience-based Design of Therapies for Substance Abuse Treatment

(Fast-Track proposals will not be accepted.)

Nanoscience and nanotechnology, by manipulating matter at the atomic or molecular levels, are emerging research areas that have the potential to fundamentally transform the study of biological systems and lead to the development of new methods for detection, prevention, and treatment of substance abuse and related disease states. NIDA invites nanotechnology-based applications in the following areas:

a) Methods to enhance the efficacy of FDA-approved compounds by reducing their size to the nanoscale range to alter absorption, distribution, metabolism, or excretion.

b) Development of new compounds, through manipulation of matter at the atomic or molecular levels, that could more readily pass the blood-brain-barrier or cell membranes.

c) Development of nanoscale particles for controlled targeted delivery of therapeutics, genes, or antibodies.

d) Expedited drug development through biomolecular analysis and characterization.

e) Application of nanostructures (e.g. noble metal nanoparticles, quantum dots, and nanolithographic structures that show promise for diagnostic development) for identification and analysis of genes, proteins, and other biological molecules implicated in the actions of drugs of abuse.

Proposals are invited from any of the above areas. Phase I should demonstrate convincingly the viability of the proposed innovation, whereas Phase II should carry out the development, characterization, testing, and screening of the innovation.

076 Development Of Science Literacy Materials Or Programs

(Fast-Track proposals will be accepted.)

The purpose of this proposed SBIR project is to develop projects or programs to improve science literacy among the general public. For many years public science literacy has remained low. Yet it remains important to the mission of NIDA that the general public and other groups are scientifically literate. It is particularly important to NIDA that all members of society understand the role of science, biology, and technology as they relate to neuroscience and drug abuse and addiction research. There is a lack of public understanding of behaviors that increase the risk for drug abuse, the use of animals in drug abuse related behavioral and biomedical research, and the necessity for basic research to make progress toward improving health. Furthermore, there is a substantial misunderstanding about the nature of addiction as a biologically based brain disorder. To address all of these issues, it is imperative that efforts be made to educate the general public and other groups about the science of addiction.

Therefore to address these issues this contract solicitation seeks innovative projects or programs that will substantially improve scientific literacy among the general public. Programs or projects must seek to improve general scientific literacy with a specific focus on drug abuse related research. Programs or projects should be directed to increasing the knowledge of the general public of scientific terms, concepts, reasoning, as well as their

ability to understand scientific public policy issues. An evaluation component must be included that can provide useful and accurate information on the efficacy of the program or project.

Phase I should include studies to determine the best format, studies that demonstrate feasibility, and the development of a prototype.

Phase II should include continued formative evaluations to guide the development of the program or project, development of the program or project, and a summative evaluation to determine the project/program's efficacy in improving science literacy.

077 Development of Serious Games for Neuro-Rehabilitation of Drug-Induced Cognitive Deficiencies

(Fast-Track proposals will be accepted.)

Neurocognitive deficits are generally drug-specific. For example, chronic methamphetamine abusers lose their decision-making ability, and suffer attentional bias in a visual discrimination task. Cocaine abusers lack cognitive flexibility, the ability to use feedback to monitor/change behavior, have slower reaction times on match-to-sample and increased errors (both omission and commission) along with attention/concentration deficits. Chronic use of opiates produces an increase in auditory, visual, and associative reaction times, impaired vigilance, attention, information processing, short-term visual memory, delayed visual memory, short-term verbal memory, long-term verbal memory and problem solving. Although in controversy, marijuana may decrease one's ability to focus, sustain, and shift attention as well as decrease memory and motivation.

The purpose of this solicitation is to support initiatives to create serious games (i.e., developing games for non-entertainment purposes) for the neurological retraining of drug-induced cognitive deficits.

Health-related gaming is an emerging industry useful in a variety of research-related, therapeutic and instructional settings. By involving a person in a computerized situation, designed to be both entertaining yet directive in the sense of covertly shaping desired behaviors, a highly flexible and programmable set of scenarios can be created. These altered behaviors can be produced by pre-programming consequences to counteract and potentially reset undesirable neurobiological and neurobehavioral deficits associated with chronic drug abuse.

Serious games can provide a completely controlled, noninvasive, safe and alternative methodology for a variety of important studies of drug abuse and addiction.

It is hoped that changes in behavioral contingencies (for example, designing a game that involves differential rates for low responding (DRL) schedule may alter brain activity (pattern changes noted using state-of-the-art neuroimaging techniques) and, thus, correlate with the improvement of neurocognitive deficits

078 E-Health Applications of Empirically Supported Therapies in English and/or Spanish

(Fast-Track proposals will not be accepted.)

The purpose of this solicitation is to encourage the development of computer and particularly internet-based treatment applications for behavioral treatment strategies for drug abuse or HIV risk reduction among people seeking drug treatment.

Although researchers have developed a number of empirically supported behavioral treatment approaches for drug abuse including counseling strategies, behavioral interventions, and psychotherapies, drug abuse treatment providers have not widely adopted these approaches. The level of clinical skill needed to administer many empirically supported treatments is high. The amount of time required is often incompatible with the usual care that many treatment programs provide. And clinics often do not have the budget to provide complex clinical training and supervision needed to master these therapies. However, computer technologies potentially can provide a more cost-effective way of speeding the translation of research-based drug abuse treatments into community settings, by allowing computer or internet-based skills training programs to augment the usual care clinicians provide. Additionally, programs available over the Internet may provide treatments directly to individuals who have barriers to receiving face-to-face treatment, such as people lacking transportation or the physical health to travel to treatment. Finally, many individuals who are native Spanish speakers may not yet have encountered empirically supported drug abuse treatments because the existing computer and web-based programs are available in English only.

NIDA currently has an active program of research computerizing aspects of Dialectical Behavior Therapy, Cognitive Behavioral Therapy, and The Community Reinforcement Approach. Phase I will develop and test the feasibility computer or web-based applications of those interventions or components of interventions with substantial research support (at least one well controlled randomized trial) for which computer applications have not yet been developed. Phase II would involve further development of those technologies that were successfully pilot tested in Phase I and the testing and evaluation of those technologies in applied clinical settings. Proposals that translate into Spanish and efficacy test technology-based interventions for native Spanish speakers are encouraged for interventions that are not incompatible with Hispanic-American culture.

079 Development of State-of-the-Art Mechanisms for Epidemiological Research

(Fast-Track proposals will be accepted.)

The purpose of this proposed SBIR project is to encourage the development of state-of-the-art mechanisms that facilitate the administration of data collection instruments in community settings using emerging assessment technologies such as hand-held computers, voice recognition via telephone, and internet-based measures.

There are numerous paper- and computer-based instruments for measuring drug abuse and its risk factors and consequences. There is a growing need, however, for technological advances that facilitate the administration of instruments in community settings using emerging assessment technologies (e.g., hand-held computers, voice-recognition via telephone, internet-based measures). The development of such technologies could facilitate real-time data collection and improve the efficiency of data transfer from respondent to researcher. This initiative encourages the development of both software and hardware to facilitate data collation, including the development of interfaces or the tailoring of widely-used instruments as well as the development of innovative new methodologies.

Phase I would involve the development and pilot testing of the new technology. Phase II would involve widespread testing and the development of manuals and other support materials.

080 Training and Infrastructure Development for Community Coalitions

(Fast-Track proposals will be accepted.)

Anti-drug coalitions are active in communities throughout the United States, however there is a dearth of materials and tools specific to community coalitions and their members available for training and infrastructure development and support. Thus, research is needed to develop and test training materials and strategies appropriate for coalition leaders, members and other volunteers involved in the coalition movement. In particular training modules and materials that address issues likely to confront coalitions need to be developed, pilot tested, revised and produced. Module content could include topics related to coalition organization formation and management; development of sponsorship relations; decision-making strategies that promote action; assessment of community needs; matching community needs to programming and strategies; promotion of unified messages; and assessment of the on-going the impact of coalitions. To accomplish these goals with optimal impact, research is needed to determine elements that contribute to the successful development of sustainable training infrastructures over time.

Phase I, the Contractor will develop, pilot test, and revise based on pilot results training materials and modules appropriate to the activities of community coalitions. Existing and relevant empirically-based knowledge would be documented and incorporated into these analyses. The pilot and revised instrument would be developed and made available.

Phase II, the Contractor will produce products: (1) for community coalition training, including modules and materials that recognize and incorporate information appropriate to community diversity; (2) that identify concrete strategies that elucidate strategies that solidify relationships with organizations and that have the potential for sustainable training infrastructure for coalitions; and (3) develop on-going systems for feedback and improvement to activities 1 and 2.

081 Clinical Trials for Anti-addiction Medication Development

(Fast-Track proposals will be accepted.)

NIDA seeks to improve its ability to identify targets, understand better underlying mechanisms of action, and eventually test in clinical settings, novel compounds or medications marketed for other

indications as candidates for further development. Many such candidates show initial promise in laboratory tests but lack pilot data needed to attract support for full-scale clinical testing. Of particular interest are candidate compounds, or marketed drugs, with potential indications targeted at abuse of cocaine, methamphetamine, and marijuana. Appropriate for consideration would typically be FDA Phase 1 studies. FDA Phase 2 studies could be conducted on marketed medications with well characterized safety profiles based on approved indications for other conditions.

Phase I of the SBIR project would be expected to result in a final protocol suitable for implementation during SBIR Phase II. If acceptable protocols are devised in Phase I, Phase II will support the conduct of small clinical trials seeking to produce data needed to support decisions to pursue full clinical testing with NIDA, or other support.

The intended product(s) of the project will provide NIDA with data essential to advancing promising new pharmacotherapies for conditions currently without adequate treatment options.

082 Development of Novel Drug Delivery Systems for Treatment of Drug Addictions

(Fast-Track proposals will be accepted.)

NIDA is seeking SBIR contract proposals on innovative and novel dosage form development to improve the effectiveness and/or minimize the abuse potential of pharmacotherapies for drug abuse/dependence. The pharmacotherapeutic agents of interest include, but are not limited to, buprenorphine and delta-9-tetrahydrocannabinol (THC). Buprenorphine has been approved for the treatment of opioid dependence. Sustained-release formulations that reduce the dosing frequency to once a week or once a month would be expected to improve compliance thus effectiveness of treatment. THC has been shown to alleviate marijuana withdrawal symptoms and thus has potential for treating cannabinoid dependence. However, the absorption of THC administered orally is poor and variable. In addition, it also requires drug administration several times a day. Formulations to improve bioavailability and reduce dosing frequency would be expected to improve the therapeutic effectiveness of THC.

In Phase I, the contractor is expected to demonstrate the feasibility of the dosage form by formulating a prototype dosage form based on biopharmaceutical and pharmaceutical rationale. In Phase II, the contractor will carry out pharmacological, toxicological and pharmacokinetic evaluations. The contractor is expected to provide a GMP scale-up of a stable dosage form with acceptable *in vitro* and *in vivo* bioavailability in animal models or in humans.

083 Create High Quality Feeder Layer Independent C57BL/6 Mouse ES Cells and Other Inbred ES Lines for High-throughput Gene Targeting

(Fast-Track proposals will be accepted.)

Gene targeting and insertional mutagenesis into mouse embryonic stem cells (ES) has revolutionized mouse genetics. Using gene targeting and gene trapping strategies mice with a desired genotype can be produced. ES cells with the desired mutation are injected into mouse blastocysts. If the ES cell, which can develop into any cell type, develops into germ line cells (those that give rise to sperm and egg), then the mutation can be transmitted to the next generation of mice.

One of the limitations of the current technology is that most of the high quality available ES cells are derived from strains of 129 derived mice. Thus, the first generation of mice carrying the mutation is in a 129 inbred background. In breeding though ten generations, requiring up to three years to make, are then needed to place the mutation on another background. This is both expensive and labor intensive.

Thus, there is a need to create high quality ES cells from other inbred background strains. Highest priority is given to developing and improving the quality of C57BL/6 ES cells for gene targeting and gene trapping because this is the background most frequently used by immunologists and neuroscientist. The C57BL/6 strain is also the most commonly used mouse for scientific research. At the same time the development of other high quality mouse ES cells in different inbred backgrounds is also highly desirable.

084 Develop Methods for Stimulating International Research Collaborations

(Fast-Track proposals will be accepted.)

NIDA supports basic, clinical, and applied research on topics ranging from genetics and neurobiology to models of service delivery. NIDA also supports rigorous international research, primarily through

various collaborative relationships between NIDA grantees and foreign scientists on these topics. The science-based information generated contributes to improving the scientific knowledge base as well as U.S. and international efforts to develop, adopt, and evaluate programs that effectively address drug abuse and its consequences. The nature of collaborative research will continue to require extensive personal contact between potential partners, but the NIDA International Program is interested in using cost-effective technologies such as the Internet to help NIDA-funded scientists and their colleagues from other countries identify possible research partners, exchange information, and develop collaborative research programs.

The NIDA International Program expects that the technological solutions might include, but not be limited to: 1) guidance on using NIDA and NIH mechanisms to identify potential research partners; 2) search engines that would categorize research by such areas as common scientific classifications (with subcategories), geographical location, drug of abuse, or methodology; 3) guided interactive discussions to encourage preliminary inquiries and information exchanges; 4) tutorials (or links to existing tutorials) on such topics as formulating research questions, building a research team, funding resources for international research, human subjects regulations, grant writing, and statistics; and 5) online critiques to help users refine their research plans and proposed partnerships.

Phase I would explore the practicality of technological solutions for forging international collaborations. Selected technologies would be developed and pilot tested. Phase II would involve further development of those technologies that were successfully pilot tested in Phase I.

NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH)

The mission of the National Institute of Mental Health (NIMH) is to reduce the burden of mental illness through research on the mind, brain, and behavior. Mental disorders constitute an immense burden on the U.S. population, with major depression now the leading cause of disability in the U.S., and schizophrenia, bipolar disorder, and obsessive-compulsive disorder ranked among the ten leading causes of disability. NIMH also takes the lead in understanding the impact of behavior on HIV transmission and pathogenesis, and in developing effective behavioral preventive interventions. The NIMH conducts a wide range of research, research training, research capacity development, as well as, public information outreach and dissemination to fulfill its mission.

This solicitation invites proposals in the following areas:

044 Interactive Web-Based Networking Tool For Linking Services And Interventions Research Training And Education Programs

(Fast-Track proposals will not be accepted.)

The purpose of this SBIR contract is to develop a sustainable, web-based networking tool that will facilitate collaborative relationships among DSIR (Division of Services and Interventions Research, NIMH http://www.nimh.nih.gov/dsir/index.cfm) supported research training, career development and education programs and permit the sharing of educational, operational, career development and research information in a safe interactive environment. The ability to share resources is of critical importance in areas of high public health need (e.g., suicide, geriatric mental health, child mental health effectiveness and interventions research, interventions and services research for children/adolescents/adults with autism, rural mental health, underserved populations, bipolar disorder, etc., social work research) where opportunities to participate in highly specialized training programs or with a handful of highly accomplished senior researchers are limited. Key to the networking tool is the innovative use of content in formats most suitable to junior researchers (pre, post doc and junior faculty). During Phase I a prototype networking tool, content specification (including sample modules)and implementation plan will be developed that is appropriate for mental health interventions and services research training programs. The prototype should be based on and suitable for use by DSIR-supported programs, but be broad, generalizable and flexible enough to assure marketability in other research training venues. DSIR's training and education programs provide an excellent opportunity to develop and test a model among programs that have diversity (e.g., systems, level of expertise, needs) yet are united by common goals).

For the purpose of this SBIR, training, education and career development refers to the following: institutional (T32) and individual (F series) research training grants; short-term educational training grants(R25) and career development (K01, K08, K25, K23, K24 and K02)grants. Information about

the Division of Services and Interventions Research can be found at http://www.nimh.nih.gov/dsir/index.cfm. Information about ongoing training, education and career development programs is available through the NIH CRISP system (http://crisp.cit.nih.gov/). General information about NIMH training programs is available at: http://www.nimh.nih.gov/grants/training.cfm.

To meet the goal of this solicitation, the web-based tool should focus on a specific content or theme (e.g., geriatric mental health interventions and/or services, child mental health interventions and/or services, clinical trials, suicide prevention, diversity and the development and adaptation of culturally appropriate interventions and services, mental health economics, etc.) or specific populations of trainees (e.g., social workers, mental health economists, psychiatrists). Innovations could include the linking of leading investigators and fellows/junior researchers in real time; an interactive archive; the capture and reformatting of workshops, seminars and grand rounds by leading investigators; online statistics and research design workshops in specific targeted areas; and interactive online career development support activities. For example, individuals with mid-level career awards, such as the K24, could host online consultations with mentees or groups of mentees. In addition, specific training programs could make course content available, link trainees, or provide “courses of excellence” via the site. Since there are several training and education programs that send fellows to diverse sites, the web-based tool should provide a structure to assure that program and fellows/junior faculty are routinely linked for scientific, mentoring and administrative activities. For example, an application that focuses on networking for the development of social work researchers might include *research content topics* (e.g., as stages of intervention development, testing and manualization of interventions, services research including cross-systems collaboration, community integration and rehabilitation, and development and adaptation of culturally appropriate interventions and services, social work practice research), *research process topics* (e.g., developing interdisciplinary research collaborations, community based research collaborations) and *research operational topics* (e.g., infrastructure development as it relates to training and development).

The composition of any proposed advisory committee should include training directors and other relevant staff, experts in the field (particularly individuals with senior or mid-level career development awards), current and past fellows/trainees, and individuals with expertise in adult education/CME credits.

To be responsive to this request, the proposal must demonstrate all of the following: (1) the ability to recruit and gain participation of appropriate experts in the relevant scientific and disciplinary, research training and career development; (2) the ability to recruit and gain participation of appropriate stakeholders; (3) well-thought out and feasible processes to assure that feedback from experts and stakeholders is integrated into all aspects of the product; (4) knowledge of the needs of end-users; (5) awareness of potential barriers to participation and sensitivity to potential issues regarding intellectual property and industry supported educational materials (e.g., inclusion and exclusion guidelines); (6) technical expertise and experience in web-facilitated education/training (including evidence of the ability to match technology to content and user need); (7) expertise in adapting information presented at scientific meetings (including research career development workshops, meetings, grand rounds etc.) into appropriate educational formats for individuals at different stages of their research training/career development and under different conditions (e.g., single users, multiple linked users and groups (e.g., classes); (8) knowledge and understanding of the specific research training needs of mental health interventions and/or services researchers and a strategy to address these needs which is relevant to the specific topic/group for whom the product is directed; (9) plans, as appropriate, for addressing the needs of fellows/junior faculty who are at geographically diverse locations from their primary training site or mentor (e.g., including ways that scientific, career development, monitoring, mentoring and administrative issues can best be handled); and (10) the provision of an in-depth discussion and rationale for selecting the particular theme/population of focus.

Two or three meetings with NIMH staff may be proposed for orientation and presentation of draft prototypes. Since the degree of complexity of this project may require more than 6 months to complete, the offeror should clearly identify the amount of time and support needed to complete their proposed scope of work.

051 Multi-Media Training and Education Materials for Cost-Effectiveness Analysis and/or Pharmaco-economics in Mental Health Services Research

(Fast-Track proposals will not be accepted.)

The past several decades of public health policy research have seen significant advances in mental health economic theory, analytic techniques and methods. Unfortunately, due to the relatively small number of individuals doing this highly specialized research, efforts to train others and disseminate methods has been limited. The purpose of this contract is to develop training and educational courses, materials and modes of delivery (e.g, classroom courses, internet, video, CD ROM etc) for an Introductory/Intermediate level educational course that will equip mental health services and interventions researchers to incorporate well-designed cost-effectiveness analysis/pharmaco-economics into their research studies and/or to develop pharmaco-economics courses for post-doc or junior faculty engaged in mental health services and interventions research.During Phase II different training strategies, or combinations of strategies, will be evaluated for their effectiveness with different user populations.

The goal of the course is to provide clinical services researchers (including, but not limited to, psychiatrists, psychologists, social workers, psychiatric nurses, pharmacists) and other interested professionals (including health policy and non-specialty mental health economists) with a comprehensive overview of basic assumptions and methodology of cost-effectiveness analysis in mental health services and interventions research and or pharmaco-economics. The general course objectives should include (but are not limited to): a review of the concept of C/E analysis in mental health services research; a presentation of the basic components of a well-designed study; recommendations/strategies about how to integrate economic evaluation into clinical services research studies and to develop interdisciplinary research approaches. The course must include components on special populations (children and adolescents, geriatrics, co-morbidity, caregivers etc.) and settings (primary care, schools, court systems, nursing homes, etc.) and be suitable for researchers engaged in or planning research careers in mental health prevention, interventions and services research. At a minimum, the proposed training and education curriculum should include materials from the March 10, 2003 Pre-Conference Methods Workshop on, “Economic Analysis of Alcohol, Drug and Mental Health Treatment Services: Lessons from The Field”. This pre-conference was organized as part of the NIMH/NIAA/NIDA supported conference, “Beyond the Clinic Walls: Expanding Mental Health, Drug and Alcohol Services Outside the Specialty Care System” (www.nimh.nih.gov/events/mhsrconf2003.cfm). Adaptation of other teaching methods of C/E analysis specifically for mental health services researchers is encouraged (e.g., University of York model). Pharmaco-economics courses in mental health should draw on the latest funded research (NIMH supported research available through a CRISP data search).

To be responsive, the proposal must provide information on the following: the purpose of the course and the needs of the proposed target audience; program schedule and description; primary faculty; and a plan for evaluating materials and strategies. Specific mental health examples must be provided. Any advisory board should include multiple end users, experts in mental health and economics and adult education. Two or three meetings with NIMH staff may be proposed for orientation and presentation of draft prototypes. Since the degree of complexity of this project may require more than 6 months to complete, the offeror should clearly identify the amount of time and support needed to complete their proposed scope of work.

052 Interactive Tools for State Mental Health Agencies around the Implementation of Evidence-Based Practices

(Fast-Track proposals will not be accepted.)

The purpose of this SBIR contract is to develop interactive, multimedia tools for state mental health agencies to better understand and move toward the implementation of evidence-based mental health practices within their states. The prototype should be based on the results of interventions and services research, particularly focusing on the knowledge base around the implementation of evidence-based interventions throughout complex state mental health and other relevant systems (e.g.: school-based interventions).

Over the past several years, state mental health directors have become increasingly interested in the use of evidence-based treatments to provide better care for their populations, as well as potentially reduce harmful variation in treatment and contain

treatment costs. NIMH and the Center for Mental Health Services, SAMHSA have sponsored two recent RFAs to facilitate state-led research on implementation (http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-05-004.html) to help ensure that the evidence on interventions is relevant to state mental health agencies and administrators and providers in the public sector. In addition, many interventions have been empirically validated without sufficient attention of the unique information and systems factors that state agencies must address when choosing to implement treatments or services state-wide. This contract will be used to develop interactive materials that assist decision-making towards implementation of evidence-based practices for specific end users—state mental health employees at different levels.

Tools supported by this contract can also include those developed to allow employees at multiple state mental health agencies to interact with each other to learn from experiences with implementing evidence-based practices. In addition, strategies for allowing dialogue between state mental health personnel and academic researchers must be included. This dialogue is intended to inform both the implementation and academic research processes, in the spirit of public-academic collaboration. Tools may include web-based bulletin boards, "listservs," real-time chat rooms, streaming video, and other interactive applications. Attention must be paid to privacy and confidentiality issues. The offeror may wish to propose varying levels of access to these tools, as well as express how the tools might be used for research that responds to the NIMH program announcement on Dissemination and Implementation Research (http://grants.nih.gov/grants/guide/pa-files/PA-02-131.html).

To be responsive to this announcement, the proposal must demonstrate an in-depth knowledge and experience with: (1) the evidence base on mental health interventions, specifically as applied to the requirements and capacity of state systems to integrate these interventions into their public mental health systems; (2) knowledge and expertise of state-level policymaking, including organizational, financial, and professional characteristics; and (3) technical expertise in developing appropriate multiple approaches/strategies (e.g. Web design, audio/video chat rooms, etc.), (4) plan to assure the accuracy and security of information and its update; and (5) demonstrate the ability to recruit appropriate expertise, including services and interventions researchers.

Two or three meetings with NIMH staff may be proposed for orientation and presentation of draft prototypes. Since the degree of complexity of this project may require more than 6 months to complete, the offeror should clearly identify the amount of time and support needed to complete their proposed scope of work.

053 Development/Adaptation of Tools and Monitoring Systems for the Implementation of Scientifically-Based Interventions and Engagement Strategies to Reduce Mental Health Problems

(Fast-Track proposals will not be accepted.)

Scientific studies have supported the effectiveness of multiple interventions that target the reduction of mental health problems and the engagement of individuals within the mental health system (McKay 2005; McKay & Bannon, 2004; Bruce et al 2002; Hoagwood & Olin, 2002; McKay 2005). Yet, many of these interventions are not widely implemented within the intended community contexts (e.g., schools, community mental health centers, justice). The purpose of this contract is to: (1) develop both the tools and a monitoring system for the implementation of scientifically-based interventions (preventive, treatment, engagement); and/or (2) adapt existing evidence based tools and systems for broader dissemination (preventive, treatment, engagement). This system should facilitate the uptake of such interventions for implementation within community-based settings.

Effective implementation processes should include two components: 1) the development/adaptation of tools to facilitate community implementation, and 2) the development of a system for ongoing training, supervision, and monitoring fidelity and outcomes. Development and implementation of these systems should include collaboration with the intervention developers and community stakeholders.

Phase 1 Tool Development activities might include:

- Adapting research based manuals for community use. Such manuals should include core implementation features (e.g., costs, qualifications of key personnel, necessary resources and time allocation) as well as supervisory protocols. Where manuals were originally developed for community use the adaptation should focus on improving usability and development of multiple methods of deliver (e.g., multi-media, CD-ROM, Web-based)

- Developing feasible intervention fidelity measures for monitoring implementation within community settings
- Developing training protocols tailored to diverse community providers
- Developing a system by which program fidelity and outcomes are monitored (e.g., web-based; observational). Such systems should include a process for generating site-specific feedback on outcomes and fidelity (e.g., site-specific data reports).

Phase 2 System Implementation Processes might include:

- Developing a standardized model for ongoing community collaborative intervention implementation
- Implementing training protocols with diverse community providers and program supervisors
- Pilot the use of the program fidelity and outcome use system. This system should incorporate measures for fidelity and program outcomes.
- Developing a systematic procedure for helping community sites maintain program fidelity and positive mental health outcomes

Two or three meetings with NIMH staff may be proposed for orientation and presentation of draft prototypes. Since the degree of complexity of this project may require more than 6 months to complete, the offeror should clearly identify the amount of time and support needed to complete their proposed scope of work.

056 Families as Research Partners: Development of Interactive Educational and Dissemination Modules to Train Family Members of Older Adults with Emotional or Behavioral Disorders about Mental Health Research Methods, Procedures, Data Analyses, and Interpretation

(Fast-Track proposals will not be accepted.)

The purpose of this contract is to develop evidence based interactive educational and dissemination modules to train families of older adults with emotional or behavioral disorders on research issues relating to studies on mental health treatment and preventive interventions and services research. The target population is broadly defined as families of older adults (spouses, adult children, grand children, aging parents of older mentally ill adults, etc.) with specific psychiatric disorders, as well as behavioral or emotional problems secondary to chronic medical illness. Because families are pivotal members of any treatment or intervention team, offering unique perspectives on the older adult's functioning and response to interventions, facilitating adherence to treatment and/or participating in aspects of an intervention, it is important that they be fully involved as partners in the development and delivery of care. Often this is not the case, particularly with minority or rural families for whom there may be cultural, language and economic barriers. Full participation may be limited by the fact that family members (or some family members) may be distance caregivers, have multiple-care giving roles or have their own health problems. In some cases, family participation is complex because multiple family members are serially or simultaneously involved with aspects of care or do not understand the research process.

Anticipated outcomes for Phase I include the development of draft: (1) interactive training materials; (2) evaluation/outcome criteria; and (3) protocols for the testing of these modules. Particular attention should be paid to developing appropriate materials and strategies to engage underserved minority, urban and rural families as well as families with disabilities in this process.

Among the modules needed are those that address issues such as: *(1) understanding and developing participatory research partnerships; (2) understanding research design, methods and procedures for services and clinical epidemiology research; (3) understanding and interpreting data analyses and research results (including research findings in the popular press) and (4) understanding evidence based treatment within a clinical context.*

The products created under this contract should recognize the diversity of families in terms of age, racial/ethnic minority status, socio-economic status, rural or other environmental factors, diversity of family types (e.g., family configuration) and special family situations that might impact training and research participation (e.g., mental health of other family members) and address specific ways these factors will be taken into consideration (e.g., focus groups). Phase I should be limited in scope, with a specific target population defined. Families should be recruited in order to obtain a representative sample of the overall stakeholder population. Content area should also be defined and tailored to

the target problems; as well as contextual variables of the families (e.g., age, ethnicity, education level, rural/urban residence); and types of intervention or services research approach (e.g., prevention, treatment, organizational, consumer preference studies). Specifics about the training modules (e.g., number of sessions, specific modifications of existing products, evaluation criteria) should be included in the proposal and should be based on empirically validated adult education processes. It is expected that an advisory group comprised of family stakeholders, individuals with expertise in adult education and funded researchers in relevant geriatric mental health areas will be included. Plans should be included for one or two trips to the NIMH for orientation and to present draft materials to program staff.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

The NHLBI plans, conducts, fosters, and supports an integrated and coordinated program of basic research, clinical investigation, and trials, observational studies, and demonstration and education projects. The Institute's mission includes studies related to the causes, prevention, diagnosis, and treatment of heart, blood vessel, lung, blood, sleep disorders, and blood resources management. Studies are conducted in its own laboratories and by other scientific institutions and individuals supported by research grants and contracts. The NHLBI SBIR program fosters basic, applied, and clinical research on all product and service development related to the mission of the NHLBI.

This solicitation invites proposals in the following areas.

031 New Technology Development for Global Assay of Blood Coagulation

(Fast-Track proposals will be accepted.)

It is currently estimated that about half of the population in the US and Europe will die from diseases related to the formation of a blood clot in a vital organ. Depending on the organ affected, the clinical condition may be described as a heart attack, stroke or thromboembolic disorder, but the underlying source of the disease is a blood clot and the subsequent tissue damage. Formation of a blood clot is a complex process. It involves a cascade of reactions between several plasma proteins called clotting factors. These interactions are controlled by activators and inhibitors. The cellular components - platelets, leukocytes and endothelial cells - intimately participate and regulate the coagulation process. There are also modifiers and significant redundancy in the system. Coagulation is complicated but it is a precisely regulated biological process; a shift in the equilibrium may cause thrombosis or bleeding with serious consequences.

There are excellent assays to measure the concentration or activity of a single coagulation protein. Similarly, there are laboratory and clinical procedures to determine the hemostatic status of parts of the clotting pathway. However, because of the complexity and multiple regulations, these assays have only limited values in predicting either thrombotic or bleeding risk in a patient. The emergence of novel technologies, and improved data handling capability, have created opportunities for developing instrumentation for the rapid measurement of a large number of parameters involved in coagulation utilizing a small volume of blood. It may now be possible to develop models that can accurately predict the thrombotic or bleeding risk in an individual and thus customize therapy based on patient profiles.

The goal of this proposal is to develop methods and instrumentation utilizing modern technology that can rapidly and accurately predict the hemostatic status of an individual. The ultimate market for this technology will be hospitals, clinical laboratories and medical centers.

Phase I should address the initial development of technology, novel assays, and data analysis capability for a global assay of human hemostatic factors.

Phase II should entail application and verification of the above technology in a patient population with established bleeding or thrombotic risk. Examples of disease areas that could be considered for technology evaluation are von Willebrand Disease or the hypercoagulable states associated with heart disease, stroke, or venous thrombosis. These developments will require a multidisciplinary team approach with expertise in fields such as hematology, bioengineering, and biostatistics.

033 Develop and Test a Diagnostic Tool for von Willebrand Disease

(Fast-Track proposals will be accepted.)

Von Willebrand Disease (VWD) is a heterogeneous bleeding disorder that is caused by a decrease or abnormality of the plasma protein, von Willebrand

factor (VWF). It is believed to be the most common hereditary bleeding disorder with an estimated prevalence of 1 percent in the US population. VWD affects both males and females, but there is a higher frequency of bleeding complications in women of child bearing age due to the challenges of menses, pregnancy and childbirth. The clinical manifestations and the severity of the disease show considerable variation even among the members of an affected family or during the lifetime of an individual. There are rare types of VWD in which life-threatening bleeding may occur but the most common symptoms are mild bleeding from the nose and mouth, menorrhagia, and postoperative bleeding.

Diagnosis and classification of Type 1 and Type 2 VWD are difficult, requiring a panel of laboratory tests and an evaluation of clinical features and family history. Different assays are required to measure the amount of VWF, distribution of VWF multimers, and VWF biological function. An additional complexity is the wide range in normal plasma level of VWF, from 50 U to 200 U per 100ml. Studies of VWF multimer size distribution can be done in the laboratory but the technology has not been adapted for routine clinical analysis. The functional assays (Ristocetin cofactor, bleeding time) show considerable variation and contribute to the challenges in the evaluation of patients with a mild disorder. Variability exists between laboratories, between patients and in the same patient from day to day. Therefore, there is a great need for an accurate, reliable and inexpensive test system that would provide VWF plasma concentration, multimer distribution and functional activity.

The goal of this proposal is to develop reliable and accurate diagnostic tools for VWD. Because of the complexity and variability of the disease, current testing is unsatisfactory, tedious and expensive. The ultimate market for this diagnostic tool will be hospitals, clinical testing laboratories and medical centers.

Phase I would be for the development and feasibility testing of a system for diagnosis and classification of Type I and Type II VWD.

Phase II would evaluate the VWD diagnosis and classification system and test its reliability and reproducibility for routine clinical application.

034 Simultaneous Assessment of Physical Activity and Sleep

(Fast-Track proposals will be accepted.)

Epidemiological and mechanistic studies link short sleep duration and sleep disordered breathing to a greater risk of various heart and vascular disease risk factors, but the routine assessment of sleep duration and quality has not been practical in large clinical research programs. Dual purpose ambulatory devices, equally suitable for the objective assessment of a risk factor such as physical activity, and sleep, are needed to collect data on these relationships and to decrease the feasibility barrier in studies where physiological data will be collected.

Proposals are invited to design, implement, and evaluate an approach (i.e. method, technique, a single instrument, or a single device) from which both sleep and physical activity can be assessed.

The technology should be appropriate for a wide range of free-living population-based clinical research activities including epidemiology, phenotypic characterization of behavioral traits, and clinical trials. The technology must provide a quantitative assessment with sensitivity, specificity, and validity that equals or exceeds that of existing technologies routinely used to assess physical activity and sleep. The technology should be an objective tool that can be used to distinguish differences in activity levels and differences in sleep duration and sleep quality between individuals. The approach should also be capable of assessing the effects of interventions on physical activity and sleep within individuals. The technology should be designed to operate with high reliability over periods long enough to be representative of normal daily life and with minimal discomfort and burden to the subjects. The time required to train staff to use and maintain the technology and the time and cost of field deployment should be less than or comparable to that of existing technologies. Recorded parameters should include light on and light off conditions.

The proposal should include 1) plans to develop and implement an appropriate technology (i.e. method, technique, a single instrument, or a single device); 2) plans to assess, document, and field test the sensitivity, specificity, and validity of the technology compared to existing methods using calorimetry as a reference method for physical activity and polysomnography as the reference method for sleep; 3) plans to develop and validate training programs for staff and to assess the burden on study participates; 4) plans to develop and implement software required for routine data-transfer, data exchange and portability, data quality control and quality assurance, analysis and

summary tabulation of events on primary data channels, and integrative analyses.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

NATIONAL CENTER FOR CHRONIC DISEASE PREVENTION AND HEALTH PROMOTION (NCCDPHP)

The NCCDPHP plans, directs, and coordinates programs in health promotion, chronic disease prevention, and reproductive health to enhance quality of life, improve reproductive health, and reduce the incidence of heart disease, stroke, cancer, diabetes, arthritis, obesity, oral disease, infant and maternal morbidity and mortality, unintended pregnancy, and emerging chronic diseases. NCCDPHP uses two essential criteria to prioritize its research portfolio, societal burden and disproportionate burden. NCCDPHP places high priority on chronic diseases and conditions and reproductive health outcomes that have the greatest total impact on health, longevity, and quality of life. NCCDPHP places high priority on eliminating disproportionate burden related to sex, age, race, ethnicity, geography, sexual orientation, socioeconomic status, disability, and special needs. NCCDPHP supports three primary types of applied research, research on cause (determinant research), research on effect (intervention research), and research on application and benefit (dissemination research). NCCDPHP emphasizes cross-cutting research that is participatory, accounts for social and ecological factors, and is implemented at multiple levels.

NCCDPHP has identified ten priority research areas: 1) develop new measures and research designs to strengthen the quality of research; 2) identify the underlying determinants of racial and ethnic health disparities; 3) develop and evaluate interventions to eliminate health disparities; 4) examine established and emerging risk factors for chronic disease and investigate their potential for public health interventions; 5) assess the effectiveness of policy and environmental interventions to promote health; 6) improve the processes and outcomes of health care systems; 7) develop effective communication strategies to promote health; 8) examine methods for helping people manage their own health; 9) develop and evaluate the effectiveness of population-based health promotion and disease prevention policies and programs at local, state, national, and international levels; 10) examine approaches for effectively translating successful community interventions into widespread practice. For examples of specific research questions in each of the ten priority areas, see *Setting the Agenda: CDC Research in Chronic Disease Prevention and Health Promotion*, available at http://www.cdc.gov.

This solicitation invites proposals in the following areas:

DIVISION OF ADULT AND COMMUNITY HEALTH, PREVENTION RESEARCH CENTERS PROGRAM

022 Interoperable Electronic Health Record System

The Prevention Research Centers Program (www.cdc.gov/prc) enables CDC to fund extramural research centers that add to knowledge and practice of chronic disease prevention and control. It aims to:

1. Build partnerships that draw on the perspectives and resources of diverse communities and actively partner with them.
2. Build long-term relationships for engaging communities as partners in research.
3. Work with populations having the greatest burden of disease and disability, especially people affected by adverse socioeconomic conditions.
4. Implement and evaluate interventions that help improve health outcomes.
5. Strive to develop communities' long-term capacity.
6. Disseminate successful results to comparable communities throughout the nation.
7. Promote the quality and availability of public health services through proven interventions.
8. Train and offer technical assistance to community and public health practitioners.
9. Strengthen the public health infrastructure by sharing information, offering training and technical assistance, and testing interventions for implementation.
10. Facilitate communication among public health professionals and community members through conferences, training, publications, and other means.

The Prevention Research Centers Program (PRC) (www.cdc.gov/prc) enables CDC to fund extramural research centers that add to knowledge and practice of chronic disease prevention and control. In addition, the PRC Program seeks to explore

electronic health information as a tool to aid in the prevention and control of chronic disease in communities and the health care system. "America needs to move much faster to adopt information technology in our health care system," HHS Secretary Tommy Thompson said as he released the action report [The Decade of Health Information Technology: Delivering Consumer-centric and Information-Rich Health Care] ordered by President Bush. "Electronic health information will provide a quantum leap in patient power, doctor power, and effective health care. We can't wait any longer." (http://www.hhs.gov/news/press/2004pres/20040721a.html)

The report, "*The Decade of Health Information Technology: Delivering Consumer-centric and Information-Rich Health Care*," says federal leadership can help hasten efforts to be carried out by the private sector. The report identifies four major goals, with strategic action areas for each:

- Goal 1 - "Inform Clinical Practice:" Bringing information tools to the point of care, especially by investing in information technology systems in physician offices and hospitals.
- Goal 2 - "Interconnect Clinicians:" Building an interoperable health information infrastructure, so that records follow the patient and clinicians have access to critical health care information when treatment decisions are being made.
- Goal 3 - "Personalize Care:" Using health information technology to give consumers more access and involvement in health decisions.
- Goal 4 - "Improve Population Health:" Expanding capacity for public health monitoring, quality of care measurement, and bringing research advances more quickly into medical practice.

The PRC Program is submitting this call for proposals to have a small business collaborate with an academic institution that has a track record of conducting community based participatory research, has established collaborations with a vulnerable population, and has extensive experience in health information technology to:

1) Develop an interoperable electronic health record system that is patient focused and customized to serve vulnerable populations and practitioners who work in community-based settings that often lack the infrastructure and resources to support currently existing electronic health record systems.
2) Propose a plan and conduct an evaluation of the interoperable electronic health record system with practitioners and vulnerable populations.
3) Propose strategies for effective utilization of (1) among practitioners, patients, researchers, and community health centers.
4) Propose a plan for distribution of final product(s) to practitioners, patients, researchers, and community health centers.

The significance of this proposed solicitation is that existing commercial systems are high-cost, designed for large practices, such as health systems or hospitals, and are out of reach for most community health centers. Most of the existing commercial systems focus on the “medical model” and do not capture the behavioral and psycho social data elements that are needed to intervene in chronic disease prevention and control, and makes the provision of tailored recommendations and guidance based on current health practices and the determinants of these health practices impossible. The U.S. President’s vision is to develop a nationwide Health Information Technology infrastructure that ensures appropriate information is available at the time and place of care, resulting in improved healthcare quality. The Health Information Technology strategy aimed at connecting physicians, hospitals, and consumers in every location of our country may not address some community health care settings and therefore those populations that are most vulnerable. Unless an electronic health record system is developed to meet the needs of community practices and the vulnerable populations they serve, the nation may face an expansion of the “digital divide”.

023 Software Tool for Evaluating a Patient’s Risk for Developing Chronic Diseases and Recommending Lifestyle Changes

The Prevention Research Centers Program (www.cdc.gov/prc) enables CDC to fund extramural research centers that add to knowledge and practice of chronic disease prevention and control. It aims to:

1. Build partnerships that draw on the perspectives and resources of diverse communities and actively partner with them.
2. Build long-term relationships for engaging communities as partners in research.

3. Work with populations having the greatest burden of disease and disability, especially people affected by adverse socioeconomic conditions.
4. Implement and evaluate interventions that help improve health outcomes.
5. Strive to develop communities' long-term capacity.
6. Disseminate successful results to comparable communities throughout the nation.
7. Promote the quality and availability of public health services through proven interventions.
8. Train and offer technical assistance to community and public health practitioners.
9. Strengthen the public health infrastructure by sharing information, offering training and technical assistance, and testing interventions for implementation.
10. Facilitate communication among public health professionals and community members through conferences, training, publications, and other means.

The Prevention Research Centers Program (PRC) (www.cdc.gov/prc) enables CDC to fund extramural research centers that add to knowledge and practice of chronic disease prevention and control. In addition, the PRC Program seeks to explore electronic health information as a tool to aid in the prevention and control of chronic disease in communities and the health care system. "America needs to move much faster to adopt information technology in our health care system," HHS Secretary Tommy Thompson said as he released the action report [*The Decade of Health Information Technology: Delivering Consumer-centric and Information-Rich Health Care]* ordered by President Bush. "Electronic health information will provide a quantum leap in patient power, doctor power, and effective health care. We can't wait any longer." (http://www.hhs.gov/news/press/2004pres/20040721a.html)

The report, "*The Decade of Health Information Technology: Delivering Consumer-centric and Information-Rich Health Care*," says federal leadership can help hasten efforts to be carried out by the private sector. The report identifies four major goals, with strategic action areas for each:

- Goal 1 - "Inform Clinical Practice:" Bringing information tools to the point of care, especially by investing in information technology systems in physician offices and hospitals.
- Goal 2 - "Interconnect Clinicians:" Building an interoperable health information infrastructure, so that records follow the patient and clinicians have access to critical health care information when treatment decisions are being made.
- Goal 3 - "Personalize Care:" Using health information technology to give consumers more access and involvement in health decisions.
- Goal 4 - "Improve Population Health:" Expanding capacity for public health monitoring, quality of care measurement, and bringing research advances more quickly into medical practice.

The PRC Program is submitting this call for proposals to have a small business collaborate with an academic institution that has a track record of conducting community based participatory research, has established collaborations with a vulnerable population, and has extensive experience in health information technology to:

1) Develop a software tool that can be used by the public and practitioners, which a) evaluates a person's risk of developing a chronic disease based on epidemiological research of causative factors and other influences; b) recommends lifestyles and other changes to reduce these risks based on empirical research; c) monitors compliance with the recommendations; and d) assesses the efficacy of the recommendations by tracking disease prevention and progression.
2) Develop a software application that can be used by the patients and practitioners, which a) tracks the progression of a patient's chronic disease over time using symptom checklists, lab results, and other relevant metrics; b) recommends lifestyle and other changes to help patients and practitioners manage the disease based on empirical research relative to the disease severity, duration and progression; c) monitors patient compliance with the recommendations; and d) tracks the outcomes of compliance vs. non-compliance to the recommendations for different patient groups.
3) Propose strategies for effective utilization of (1) and (2) among practitioners, patients, researchers, and community health centers.

4) Propose a plan for distribution of final product(s) to practitioners, patients, researchers, and community health centers.

The significance of this proposed solicitation is that existing commercial systems are high-cost, designed for large practices, such as health systems or hospitals, and are out of reach for most community health centers. Most of the existing commercial systems focus on the "medical model" and do not capture the behavioral and psycho social data elements that are needed to intervene in chronic disease prevention and control, and makes the provision of tailored recommendations and guidance based on current health practices and the determinants of these health practices impossible. The U.S. President's vision is to develop a nationwide Health Information Technology infrastructure that ensures personalized care that uses health information technology to give consumers more access and involvement in health decisions. Unless a personalized electronic health promotion tool is developed to meet the needs of community practices and the vulnerable populations they serve, the nation may face an expansion of the "digital divide".

DIVISION OF DIABETES TRANSLATION

024 Simplified Fingerprint Collection and Interpretation for Medical Risk Assessment

The fetal environment in early pregnancy may contribute to chronic-disease risk in later life. Dermatoglyphics – in particular, the fingertip ridge counts – can provide insights into each person's past environment during early pregnancy. Thus, basic research and public-health applications would benefit from enhanced methods to collect fingerprints and determine their ridge counts (Kahn HS. *Amer J Hum Biol* 2005;17:383). Technologies are now available for inkless collection of fingerprints, for their conversion to electronic formats, and for semi-automated ridge counting. However, these systems were developed for non-medical purposes such as criminal identification. The outputs of these existing technologies are in formats that serve poorly the needs of biological and anthropological research or of public-health applications.

The Division of Diabetes Translation solicits applications for research to develop an integrated product that would (1) collect specified fingerprint images in electronic format; (2) identify for each fingerprint the underlying pattern, core(s), and triradius point(s); (3) count the ridges that separate cores and triradius points; and (4) provide an electronic output file that includes (for each specified finger) the fingerprint pattern, radial ridge count, ulnar ridge count, and inter-core ridge count.

An optimal product should be suitable and acceptable for most subjects ranging from pre-adolescence to about 70 years old, and it should be small enough to be portable for field work. The product should permit confirmation of fingerprint image quality at the time of collection by a field technician, and it should include a mechanism by which a trained reviewer will confirm or revise the assignment of fingerprint patterns and ridge counts. The electronic outputs of the product should be compatible with anthropological conventions; the ridge counts obtained for each finger should lead directly to that finger's *net* ridge count according to existing (or future) algorithms. As dictated by on-going research, the electronic output may also compute ridge-count gradients between specified fingers (e.g., arithmetic difference between fingers 4 and 5). In the interest of protecting individual confidentiality, the output variables should avoid using conventions and systems that facilitate linkage to criminal-justice datasets.

NATIONAL CENTER FOR HIV, STD AND TB PREVENTION (NCHSTP)

The mission of NCHSTP is to provide national leadership in preventing and controlling human immunodeficiency virus, other sexually transmitted diseases, and tuberculosis by working with community, state, national, and international partners in effective multi-disciplinary programs of surveillance, research, and evaluation.

This solicitation invites proposals in the following areas:

DIVISION OF AIDS, STD, AND TB LABORATORY RESEARCH

This contract proposal solicitation has been amended to include the following 5 topics.

019 Development of Novel Genotyping Procedures for Mycobacterium Tuberculosis

The Institute of Medicine Report identified the need for better methods for genotyping of M. tuberculosis strains to facilitate and focus tuberculosis control efforts. Currently available methods are too costly, time consuming, technically demanding, or labor intensive to be applicable at the local level. This contract seeks to develop field-expedient genotyping

technology including clinical laboratory tests and accompanying instrumentation. The technology should be readily usable by staff in State and Local Public Health Laboratories. The following are particular areas of interest:

a) Development and evaluation of instrumentation to facilitate genotyping by the spoligotyping or MIRU typing methods in a cost-efficient manner.

b) Development and evaluation of new methods for genotyping M. tuberculosis strains.

020 New Laboratory Tests for Tuberculosis and Detection of Drug Resistance

In order to accomplish the Healthy People 2010 goal of reducing the time required for the laboratory confirmation of the diagnosis of tuberculosis to 48 hours, rapid tests to detect Mycobacterium tuberculosis or its products are needed. In addition, rapid tests that can reduce the turnaround-time for detection of drug-resistance are needed. This contract seeks to develop field-expedient testing technology (including clinical laboratory tests and accompanying instrumentation) to detect M. tuberculosis or its products in patient specimens and/or to determine drug resistance of M. tuberculosis isolates. The technology should be readily usable by staff in clinical and public health laboratories. The following are particular areas of interest:

a) Development and evaluation of procedures and instrumentation to facilitate nucleic acid amplification testing methods for M. tuberculosis and optimize the ease-of-use and cost-efficiency of nucleic acid amplification testing.

b) Development of rapid cost-efficient methods to detect and identify Mycobacterium tuberculosis or its products in patient specimens suitable for use in clinical laboratories.

c) Development of rapid cost-efficient methods and accompanying instrumentation to determine drug resistance of M. tuberculosis isolates suitable for use in clinical laboratories.

022 Technology to Develop Handheld Amplification Test for Sexually Transmitted Infections

There is an increasing use of amplification tests for the detection of sexually transmitted infections. More recently, conventional nucleic acid amplification tests are being replaced by updated by more recent methods such as real time PCR. Additionally, there is also a trend to develop tests that are easily useable in on-site field conditions. The Division of AIDS, STD, and TB Laboratory Research, National Center for HIV, STD, and TB Prevention, CDC is interested in funding developmental research to produce a handheld multiplex nucleic acid amplification test for the rapid diagnosis of sexually transmitted infections, on-site in clinical settings, with a high degree of specificity and sensitivity. The multiplex detection would be for two subsets of microorganisms: 1) Genital ulcer disease to include *Haemophilus ducreyi*, *Treponema pallidum*, and Herpes Simplex Virus and 2) Genital discharge disease to include *Neisseria gonorrhoeae*, *Clamydia trachomatis, Trichomonas vaginalis*, and *Mycoplasma genitalium*. The system developed needs to be rapid, inexpensive and require minimum technical experience.

023 Technology to Develop an Ambient Temperature Specimen Transport System

There is an increasing use of amplification tests for the detection of sexually transmitted infections. Therefore, an increasing problem for many local laboratories is the issue of specimen transportation. Many nucleic acid amplification tests require that a specimen be tested within 24 to 48 hours after collection or otherwise the specimen needs to be frozen. Many private or small community providers are unable to meet these guidelines. Due to this expanding problem, the Division of AIDS, STD, and TB Laboratory Research, National Center for HIV, STD, and TB Prevention, CDC is interested in funding developmental research for the production of an ambient temperature specimen transport system for use in nucleic acid amplification tests. Such a system should be able to provide a stable and adequate specimen for nucleic acid amplification tests for a time period of four to seven days. Additionally, since there are growing opportunities for specimen self-collecting, the system must also be inconspicuous and convenient for patients to transport, by mail or otherwise, to the testing laboratory. It must also meet all state and federal guidelines for the shipment of hazardous/infectious materials. The system developed must also be inexpensive and require minimum technical experience.

024 System to Concentrate and Purify Nucleic Acids from Whole Blood

Nucleic acid amplification tests are increasingly becoming the method of choice for the detection of

sexually transmitted infections. The use of whole blood as the specimen for detection of blood-borne infections such as syphilis has been hampered by the presence of amplification inhibitors and the low number of organisms/ml of blood at various stages of the disease. Attempts to concentrate the DNA present in blood specimens has also led to concentration of amplification inhibitors. Conversely, standard purification techniques often lead to inadequate nucleic acid targets. To address this issue, the Division of AIDS, STD, and TB Laboratory Research, National Center for HIV, STD, and TB Prevention, CDC is interested in funding developmental research of a system for both the concentration and purification of nucleic acid targets from whole blood to enable nucleic acid amplification. The system developed needs to be rapid, consistent, inexpensive and require minimum technical experience.

DIVISION OF TUBERCULOSIS (TB) ELIMINATION (DTBE)

021 Development of a Novel Information System for Remote TB Control and Prevention Programs

As noted in CDC's response to the IOM TB report, goal one reflects activities related to maintaining control of TB. While remarkable advances have been accomplished on the US mainland, appropriate and effective infrastructure and TB information systems to support surveillance, reporting, and patient-centric interventions have been challenging to implement and maintain in the US-affiliated Pacific Island Jurisdictions (PIJ). The PIJs are very remotely situated from the US mainland and they grapple with tremendous geographical distances within jurisdictions creating an environment which does not readily support reliable information systems.

This contract seeks to develop an information system using established standards which will enable PIJs to overcome unique conditions such as (1) the varying protocols established by WHO and CDC; (2) the lack of data communication between rural and urban health centers; (3) the inadequate internet connectivity. Proposals should reflect systems development that incorporates both non-web based and web-based solutions. Sole web-based solutions are not realistic for this region.

- Development of a system which incorporates TB data collection standards from WHO DOTS, Secretariat of the Pacific Community, and CDC
- Development of a system to provide the ability to monitor and evaluate program processes and outcomes which are useful for surveillance, reporting, prevention and control activities to ensure that patient-centered case management and monitoring of treatment outcomes are the standard of care for all TB patients in the PIJs
- Development of a system which builds the capacity of PIJ TB control programs to conduct systematic and comprehensive reviews of TB patients
- Development of a system which improves and enhances TB laboratory capabilities
- Development of a system which must work on the current software capacity (MS Office) and/or limited dial-up Internet access
- Development of a system which captures necessary patient and laboratory information yet is optimized for querying large amounts of data to support program evaluation activities and CDC reporting and monitoring requirements
- Development of a system which supports access by multiple users across multiple PIJs to allow for national data collection
- Development of a system which utilizes technologies which can be supported locally
- Development of a system which addresses the challenges of intermittent Internet access.

DIVISION OF STD PREVENTION

This contract proposal solicitation has been amended to include the following topic.

025 A Delivery System for Patient-Delivered Partner Treatment for Sexually Transmitted Disease Control

Sexually transmitted diseases (STDs) like gonorrhea and chlamydia are a major public health concern in the United States (US). These infections are of concern because of the negative sequelae, e.g., pelvic inflammatory disease, ectopic pregnancy, and infertility, they can produce and because of evidence that they can facilitate the transmission of Human Immunodeficiency Virus (HIV).

Efforts to control STDs in the US have focused on partner notification, the practice of eliciting sex partner locating information from persons diagnosed with STDs and following up with sex partners; these

efforts are usually conducted by Health Departments. The burden of STDs and a shift of STD care in the US from the public to the private sector have forced health care professionals to develop alternate strategies for STD control. One of these strategies is patient-delivered partner therapy (PDPT), a provider's practice of prescribing or dispensing medication to patients diagnosed with an STD to be administered to their sex partners. PDPT research has shown promising findings for reduced reinfection and is clinically practiced. There are, however, no widely used or standardized PDPT delivery systems available that can provide the medication in appropriate packaging that includes labeling and educational material for patients and their partners.

Phase I goals are to develop a portable, inexpensive, user-friendly delivery system that health care professionals may use to dispense medications to patients diagnosed with an STD for their sex partners. The system should meet child-proofing requirements; provide the correct storage environment for medications; and provide labeling, i.e., name of medication, dose, number of doses contained in the system, contraindications for use, follow-up instructions and major side effects. The system should also contain easily understandable STD educational material for the patient and partner and sources where the patient and/or partner may obtain additional educational information if needed, e.g., links to STD websites. The system should focus on, but not be limited to, treatments for gonorrhea and Chlamydia. The Phase I end-product will be a model of the physical delivery system.

In Phase II, the product will be piloted in clinic settings. Results from the pilot testing will be used to edit and revise the product.

GLOBAL AIDS PROGRAM

026 Technologies to Reduce Unsafe Injections and Sharps Injuries

The needle-syringe (N-S), invented 150 years ago, poses serious problems in developing countries, primarily through intentional or inadvertent unsterile re-use, as well as through needlestick injury and improper waste disposal. These pose a substantial burden in resulting transmission of human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and other blood-borne pathogens (BBP). In some developed countries, the solution has been to use sterile, disposable N-Ss only once, activate their needletip-shielding devices, and then discard each safely. In developing countries, however, where an estimated 16 billion injections are administered annually, this solution is more difficult. Logistical constraints result in interruptions in the supply of new N-Ss to remote clinics, and make more difficult maintaining proper sharps waste disposal systems. Supply interruptions and limited funds encourage improper recycling of what should be single-use-only N-S. Auto-disabling syringes used in some settings in developing countries (e.g., immunizations) do not yet have needle-shielding features, and are not yet universally available and used to prevent improper re-use. These problems extend to almost all other sharps needed to provide modern health care.

The HIV Prevention Branch, Global AIDS Program, National Center for HIV, STD, and TB Prevention, CDC, solicits proposals for research and development of appropriate and affordable technologies that may contribute towards solving the problems of unsafe injection and unsafe sharps disposal described above. Examples of such technologies -- not to the exclusion of others, which may be materials, methods, techniques, instruments, or devices – include: a) plastic needles to replace steel ones to simpify sharps disposal; b) noncorrosive sterilants without the disadavantages of bleach, or other equipment for effective sterilization of reusable medical instruments; c) locally-fueled melter ovens or other simple, practical sharps waste encapsulation or disposal systems; and d) needle-free devices for administering off-the-shelf formulations of existing vaccines and drugs routinely used or proposed for developing countries.

NATIONAL IMMUNIZATION PROGRAM (NIP)

The National Immunization Program (NIP) of CDC, plans, coordinates, directs, and participates in efforts to prevent and reduce illness and premature death through immunization against disease. Activities include: (1) conducting epidemiology, national surveillance, research and technical consultation on designated diseases for which effective immunizing agents are available, and on the safety of vaccines; (2) assessing immunization levels at national, state, and local levels; (3) guiding the development of recommendations, guidelines, technologies, and policies for effective, safe, efficient, and economical use of existing vaccines, and for the development and incorporation of new and improved vaccines and associated technologies into disease control programs; (4) providing technical, epidemiologic, scientific, statistical, financial, programmatic, and administrative assistance to state and local health departments in support of their immunization

programs to prevent diseases recommended for vaccination; (5) implementing national outreach, mobilization, and public information activities to increase understanding about the benefits and risks of vaccines, to promote the demand for them, and to improve immunization practices among health care providers; (6) designing, developing, and implementing information systems to ensure that persons are properly immunized with the recommended vaccines for them; (7) collaborating with the World Health Organization (WHO) and its regional offices and with other CDC Centers/Institutes/Offices (CIOs) in worldwide eradication efforts for polio, and in planning for eradication of other diseases.

This solicitation invites proposals for the following topic areas:

016 Develop Methods to Enhance Administration of Vaccines, Including Live Virus Vaccines, Through the Respiratory Tract

Because of the drawbacks associated with injection of vaccines using syringes and needles, development of alternate methods of vaccine administration is a research priority. We are requesting proposals for methods to enhance the delivery of vaccines through the respiratory tract. Proposals should address: 1) Respiratory delivery methods for vaccines, including but not limited to aerosols, dry powders and nasal sprays; 2) Methods for improving the uptake or effectiveness of vaccines delivered through the respiratory tract; 3) Methods for evaluating deposition of vaccines in the respiratory tract, including but not limited to computer simulation models and in vitro models; or 4) Methods for facilitating study of vaccines delivered through the respiratory tract in animal models.

019 Disposable-Cartridge Jet Injector Technology

Prompt protection of public health in response to pandemic, local or regional epidemic, or bioterror threat may require rapid vaccination of a large proportion of the population with limited health personnel. High-speed, multi-use-nozzle jet injectors (MUNJIs) in which the same orifice and fluid pathway are used on consecutive vaccinees, have been used successfully with a variety of vaccines since the 1950s, but withdrawn from public health use in the 1990s after causing a hepatitis B outbreak and accumulating data suggesting they may transmit infectious bloodborne pathogens from one patient to the next. A new generation of disposable-cartridge jet injectors (DCJIs) that avoid this concern were introduced in the 1990s, but they generally are not designed for rapid use in mass vaccination campaigns. DCJIs also offer a means for developing countries to overcome the dangers and drawbacks of using needle-syringes, including unsterile re-use, needlestick injuries, and improper disposal.

Proposals are invited for disposable-cartridge jet injector technology for affordable use in both developed and developing countries for high-speed mass campaigns and/or slow-speed, routine immunization. Proposals may be for new or improved injectors, or for associated technology, such as filling systems or accessories, auto-reconstitution of lyophilized vaccines, and other related or useful components.

Proposals that promote standardization of cartridge-injector interfaces among different companies through appropriate licensing arrangements will be given priority consideration because of the public interest in universal standards for their cartridges, which should be designed for end-user filling of existing, off-the-shelf vaccines, as well as adaptable for vaccine manufacturer pre-filling in which the cartridge becomes the primary vaccine container.

020 Development of Serologic Tests to Detect Immune Responses in *Bordetella pertussis* Infection

Pertussis is the only vaccine-preventable bacterial disease that is increasing in incidence. Diagnosis of pertussis is challenging, particularly in adolescents and adults who often present late in the course of infection when it is difficult to detect the organism. Serologic testing has used for adolescents and adults, but usually only provide late or retrospective diagnosis In addition, current serologic tests measure antibodies to antigens that are also present in the vaccines, making it difficult to differentiate clinical disease from vaccine response.

CDC is seeking organizations to undertake research leading to the identification of antigens that induce major immune responses in persons with pertussis infection rather than pertussis vaccination. These antigens would be used to develop and validate sensitive and specific serologic assays for clinical diagnostic use. The tasks will include standardization of the antigen preparation (s), development of reference reagents (including reference sera), and standardization of assays, that

could lead to validated, FDA-licensed products for in vitro diagnostic use. CDC is interested in tests for antibodies to *B. pertussis* antigens that are not present in pertussis vaccines currently licensed in the United States. The tests must distinguish immune responses to infection from immune response to vaccination.

CDC's goal is to make available tests for the detection of immune responses to *B. pertussis* infection that could be used in clinical and public health laboratories.

Proposals should focus on previous experience and current capabilities in the relevant areas. Only organizations with a strong background and recent experience developing immunologic assays should respond. The final proposal should consider: (1) usefulness of the identified antigens/antibodies in the diagnosis of pertussis using clinically relevant samples; (2) procurement of a sustainable supply of reference materials; (3) procurement of a sustainable supply of clinical samples for test development and validation; (4) development of an easy-to-use assay that is suitable for use in clinical and public health laboratories; (5) assay endpoints that can be interpreted unambiguously as 'positive' and 'negative' for the diagnosis of acute pertussis infection distinct from recent vaccination (highest priority outcome); (6) development of an assay to assess immune protection from pertussis (long term). The ultimate goal is FDA licensure of the test for in-vitro diagnostic use.

021 Development of a Rapid, Point-of-Care Test for the Diagnosis of Current Pertussis Infection

Pertussis is the only vaccine-preventable bacterial disease that has an increased number of reported cases. Pertussis is difficult to diagnose. There is a wide clinical spectrum, particularly in adults. Culture of pertussis can take up to 10 days, is sensitive only under ideal conditions, and is usually negative with even one dose of antibiotics. PCR testing is more sensitive but results are generally not available in less than 24-48 hours. Delay in the diagnosis of pertussis can result in the spread of disease to family members and other close contacts, increasing the risk for outbreaks and severe disease among vulnerable populations. Rapid tests (with results in minutes rather than days) have been useful in controlling transmission in other infectious diseases (e.g., HIV and group B strep).

A variety of laboratory tests have been developed for detection of bacterial antigens in body fluids (e.g., blood, nasopharyngeal secretions, urine). Studies with other organisms suggest that bacterial antigens are stable in secretions and are detectable much longer than bacteria remain viable. Furthermore, antigen detection can be useful even when antibiotic treatment has made culture impossible. Studies suggest that *B. pertussis* antigens (e.g., PT, FHA, adenylate cyclase, LOS) can be found in a variety of bodily fluids, including nasopharyngeal secretions and urine. Investigators have shown the presence of *B. pertussis* in NP specimens by detecting its adenylate cyclase enzyme (Confer DL, Eaton JW. Dev Biol Stand 1985;61:3-10). Boreland and Gillespie (J Clin Pathol 1984;37:950-955) detected *B. pertussis* antigens in serum and urine samples from clinically diagnosed cases.

There is a need for a rapid, sensitive and specific, point-of-care test for the detection of pertussis. The availability of a bedside test would allow immediate diagnosis and treatment of the patient and prophylaxis of contacts. Such a test would be convenient for both the healthcare provider and the patient.

The tasks of the project include: (1) identification of pertussis antigens that can be detected in bodily fluids (e.g., blood, NP secretion, urine) of persons infected with *B. pertussis*; (2) standardization of the antigen(s) preparation; (3) development of a simple, easy-to-use, rapid (minutes), point-of-care antigen test for clinical diagnostic use with acceptable sensitivity, specificity, and predictive values; (4) development of reference reagents including internal and external controls; (5) standardization of the test assay; (6) procurement of a sustainable supply of reference materials; (7) procurement of a sustainable supply of clinical samples for test development and validation; (8) assay endpoints that can be interpreted unambiguously as 'positive' or 'negative' for the diagnosis of acute pertussis infection. The ultimate goal is FDA licensure of the test for in-vitro diagnostic use.

HUMAN SUBJECTS RESEARCH GUIDANCE AND INFORMATION SUPPLEMENT

PREPARING THE HUMAN SUBJECTS RESEARCH SECTION OF THE RESEARCH PLAN

In the Human Subjects Research section of the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets (1) the requirements of the HHS regulations (45 C.F.R. Part 46) to protect human subjects from research risks, (2) the requirements of NIH policies for data and safety monitoring of clinical trails, and (3) the requirements of NIH policies on inclusion of women, minorities, and children. See Instructions Pertaining to Non-Exempt Human Subjects Research.

If the research is exempt from the requirements in the Federal regulations, you must provide a justification for the exemption with sufficient information about the involvement of the human subjects to allow a determination by peer reviewers and NIH staff that claimed exemption(s) is/are appropriate. See Exempt Human Subjects Research.

Applications must comply with this requirement; if not, application processing may be delayed or the application may be returned to the applicant without review.

For all research involving human subjects, a part of the peer review process will include careful consideration of protections from research risks, as well as the appropriate inclusion of women, minorities, and children. The Scientific Review Group (SRG) will assess the adequacy of safeguards of the rights and welfare of research participants, and the appropriate inclusion of women, minorities, and children, based on the information in the application.

To assist you in completing the Human Subjects Research portion of the Research Plan, we have provided six possible scenarios. All research will fall into one of these six scenarios. Determining which scenario best matches your proposed research depends on your answers to the following five questions:

Question 1: Does your proposed research involve human subjects?

Question 2: Does your proposed human subjects research meet the criteria for one or more of the exemptions in the HHS regulations (45 C.F.R. Part 46)?

Question 3: Does your proposed research meet the definition of clinical research?

Question 4: Does your proposed research include a clinical trial?

Question 5: Does your proposed research meet criteria for an NIH-Defined Phase III Clinical Trial?

Click on the questions and when you can answer the five questions, select the scenario that best matches your responses, and then follow the instructions provided for the scenario you choose.

HUMAN SUBJECTS RESEARCH

Question 1: Does your proposed research involve human subjects?

The first thing you must determine is whether or not your research involves human subjects, either at the applicant organization or at any other performance site or collaborating institution (e.g., subcontractors, consultants).

The research described in your application may include more than one research project; thus the application may include individual projects that meet the requirements for non-exempt or exempt human subjects research, or are not defined as human subjects research.

If research activities involving human subjects are planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution, then your answer is "Yes" even if the research is exempt from regulations for the protection of human subjects.

The HHS regulations "Protection of Human Subjects" (45 C.F.R. 46, administered by OHRP) define a *human subject* as a living individual about whom an *investigator* conducting *research obtains*:

- data through *intervention* or *interaction* with the individual or
- *identifiable private information*

Investigator: The OHRP considers the term investigator to include anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. However, if the individuals who provide *coded* information or specimens also collaborate on other activities related to the conduct of the research with the investigators who receive such information or specimens, they will be considered to be involved in the conduct of the research. [OHRP's Coded Specimen Guidance]

Research: HHS regulations define *research* at 45 C.F.R. 46.102(d) as follows:
Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Obtains: In its guidance for use of coded specimens, OHRP has determined that under the definition of human subject at 45 C.F.R. 46.102(f), *obtaining* identifiable private information or identifiable specimens for research purposes constitutes human subjects research. *Obtaining* means receiving or accessing identifiable private information or identifiable specimens for research purposes. OHRP interprets *obtaining* to include an investigator's use, study, or analysis for research purposes of *identifiable private information* or identifiable specimens already in the possession of the investigator.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. (45 C.F.R. 46.102(f))

Interaction includes communication or interpersonal contact between investigator and subject. (45 C.F.R. 46.102(f))

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record). Private information must be *individually identifiable* (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. (45 C.F.R. 46.102(f))

Individually Identifiable Private Information: According to its guidance for use of coded specimens, OHRP generally considers private information or specimens to be *individually identifiable* as defined at 45 C.F.R. 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through *coding* systems. Conversely, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research Using Human Specimens or Data:

Regulatory requirements (Federal and state) to protect human subjects apply to a much broader range of research than many investigators realize, and researchers using *human specimens and/or data* are often unsure about how regulations apply to their research. Regulatory obligations to protect human subjects would apply, for example, to research that uses –

- Bodily materials, such as cells, blood or urine, tissues, organs, hair or nail clippings, from living individuals who are individually identifiable to the investigator(s), even if these materials were collected by others;
- Residual diagnostic specimens from living individuals that are individually identifiable to the investigator(s), including specimens obtained for routine patient care that would have been discarded if not used for research;
- Private information, such as medical information, about living individuals, that is individually identifiable to the investigator(s), even if the information was not specifically collected for the study in question. This includes research on genetic information that can be readily associated, by the investigator(s), with identifiable living individuals.

The definition of "human subject" includes, but is not limited to, human organs, tissues, and body fluids from living individuals, as well as private graphic, written, or recorded information about living individuals, if (1) there is interaction or intervention with a living individual to obtain the specimens or data for research purposes, or (2) the identity of the subjects can be readily ascertained by the investigator or other members of the research team.

Research that involves only *coded* private information/data or coded human biological specimens may not constitute human subjects research under the HHS human subjects regulations (45 C.F.R. Part 46) if:

- the specimens and/or private information/data were not collected specifically for the currently proposed research project through an interaction/intervention with living individuals AND
- the investigator(s) (including collaborators) on the proposed research cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain (e.g., the researcher's access to subject identities is prohibited by written repository procedures and policies and/or through an agreement signed between the recipient researcher and the repository providing the specimens and/or data). [See definitions below and the following guidance from the Office for Human Research Protections (OHRP) for additional information and examples: http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf.]

Individuals who provide *coded* information or specimens for proposed research and who also collaborate on the research involving such information or specimens are considered to be involved in the conduct of human subjects research.

Coded: With respect to private information or human biological specimens, *coded* means that:

(1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol or combination thereof (i.e., the code); and

(2) a key to decipher the code exists, enabling linkage of the identifying information with the private information or specimens.

You may find it helpful to consult the following guidance from OHRP:

- OHRP Decision Charts: http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm
- OHRP Policy on Coded Specimens and Data: http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf
- OHRP Guidance on Repositories: http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm; http://www.hhs.gov/ohrp/humansubjects/guidance/guid1223.pdf

With regard to the engagement of performance sites in proposed human subjects research, you may find it helpful to consult the following:

- OHRP Memo on Engagement: http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm

The decisions about when research involving human specimens and/or data from subjects is considered human subjects research are complex. The OHRP recommends that institutions have policies in place that designate the individual or entity authorized to determine whether proposed research is exempt from regulatory requirements to protect human subjects and that determinations should be made by someone other than the investigator.

You need to be aware that the involvement of human subjects in non-exempt research must be approved by your IRB prior to award.

The NIH Office of Extramural Research Human Subjects website contains additional information and Frequently Asked Questions that may help investigators understand how these regulations and Guidance documents apply to their research. See http://grants.nih.gov/grants/policy/hs/index.htm.

How can you determine whether research that involves only the use of specimens and/or data from pathology archives or a specimen bank and/or data repository is human subjects research?

The research described in your application may include more than one research project; thus the application may include separate projects that meet the requirements for either human subjects research, exempt human subjects research, or are not defined as human subjects research. Examples are provided below:

- If the specimens and/or data were obtained specifically for the currently proposed research project through intervention or interaction with a living individual, then your research is human subjects research.
- If you receive or have access to individually identifiable specimens or data from living individuals (e.g., pathology or medical records), your proposed research is human subjects research.
- If you receive or have access to existing individually identifiable private information or identifiable specimens from living individuals (e.g., pathology or medical records), but you as the investigator or your collaborator record the information in such a manner that you cannot subsequently access or obtain direct or indirect identifiers that are linked to the subjects the research project that you conduct using data recorded in this manner meets the requirements of Exemption 4. If you will retain or can access any identifiers, the research project is not exempt under Exemption 4.
- If you are using specimens and/or data and neither you nor your collaborators can identify the subjects from whom the specimens and/or data were obtained either directly or indirectly through coding systems, the HHS human subjects regulations (45 C.F.R. Part 46) do not apply at all.
- If your research involves only coded private information/data or coded specimens, OHRP does not consider this research to involve human subjects as defined under the HHS Protection of Human Subjects Regulations (45 C.F.R. Part 46.102(f)) *if* the following conditions are *both* met:
    - the private information/data or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; *and*

- the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:

  (a) the key to decipher the code is destroyed before the research begins;

  (b) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased;

  (c) there are IRB approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; *or*

  (d) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

What is not human subjects research under HHS regulations at 45 C.F.R. Part 46?

- Research that does not involve intervention or interaction with living individuals, or identifiable private information is not human subjects research (see definitions),

- Research that only proposes the use of cadaver specimens is not human subjects research, because human subjects are defined as "living individuals." The use of cadaver specimens is not regulated by 45 C.F.R. Part 46, but may be governed by other federal, state and local laws.

Guidance and Additional Instructions

If you answered "No" to Question 1, then proceed to Scenario A.

If you answered "Yes" to Question 1, then you may need to determine whether your research meets the criteria for an exemption from the Human Subjects Protection requirements. Proceed to Question 2.

If you need to consider an alternative scenario, return to the Decision Table.

EXEMPT HUMAN SUBJECTS RESEARCH

Question 2: Does your proposed human subjects research meet the criteria for one or more of the exemptions in the HHS regulations (45 C.F.R. 46)?

Some human subjects research is exempt from the HHS regulations (45 C.F.R. 46). OHRP guidance states that Exemptions should be independently determined (http://www.hhs.gov/ohrp/humansubjects/guidance/irb71102.pdf). Institutions often designate their IRB to make this determination. Because NIH does not require IRB approval at time of application, the exemptions designated in item 4a often represent the opinion of the PI, and the justification provided for the exemption by the PI is evaluated during peer review.

The research described in your application may include more than one research project; thus the application may include individual projects that meet the requirements for non-exempt or exempt human subjects research, or are not defined as human subjects research.

If research activities involving human subjects are planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution, then your answer is "Yes" to Question 1 "Does your proposed research involve human subjects" even if the research is exempt from regulations for the protection of human subjects.

Research involving individuals who are or who become prisoners cannot be exempt under any exemption categories (see 45 CRF Part 46, Subpart C).

Your human subjects research is exempt if all of the proposed research meets the criteria for one or more of the following six exemptions.

Exemption 1: Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Exemption 2: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless:

(i) information obtained is recorded in such a manner that human subjects can be identified directly or through identifiers linked to the subjects and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

Exemption 2 for research involving survey or interview procedures or observation of public behavior, does not apply to research with children (see 45 C.F.R. Part 46, Subpart D), except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Exemption 3: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

Exemption 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

The humans subjects regulations decision charts (http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm) from the Office of Human Research Protection (OHRP) will help you to see whether your research falls under the human subjects regulations and if so, whether it meets the criteria for Exemption 4. See also the information contained at: Exemption 4 Guidance and Information.

The NIH Office of Extramural Research website also contains information that is helpful for determining whether your human subjects research meets the criteria for Exemption 4. See http://grants.nih.gov/grants/policy/hs/index.htm.

Research that meets the criteria for Exemption 4 is not considered "clinical research" as defined by NIH. Therefore the NIH policies for inclusion of women, minorities and children in clinical research do not apply to research projects covered by Exemption 4.

Exemption 5: Research and demonstration projects that are conducted by or subject to the approval of Department or Agency heads and that are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs (ii) procedures for obtaining benefits or services under those programs (iii) possible changes in or alternatives to those programs or procedures or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

Exemption 6: Taste and food quality evaluation and consumer acceptance studies (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Guidance and Additional Instructions

If you answered "Yes" to Question 2, then your research meets the criteria for an exemption.

- If your research meets the criteria for Exemption 4, then follow the instructions for Scenario B and read the information contained in Exemption 4 Guidance and Information.
- If your research meets the criteria for any of the other five exemptions, follow the instructions for Scenario C.

Remember that you need to identify which exemption(s) you believe is applicable to your research, and provide a justification for the exemption(s) with sufficient information about the involvement of human subjects to allow a determination by peer reviewers and NIH staff that the claimed exemption(s) is appropriate.

If you answered "No" to Question 2, then your research does not qualify for one of the exemptions, and your research is not exempt from full IRB review. Proceed to Question 3.

If you need to consider an alternative scenario, return to the Decision Table.

CLINICAL RESEARCH

Question 3: Does your proposed research meet the definition of clinical research?

The NIH defines Clinical Research as:

(1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies.

(2) Epidemiologic and behavioral studies.

(3) Outcomes research and health services research.

Clinical research that does not meet the criteria for a clinical trial or an NIH-defined Phase III clinical trial must follow the instructions in Scenario D.

Research projects that meet the criteria for Exemption 4 are not considered "clinical research." Investigators who propose research that meets the criteria for Exemption 4 must follow the instructions provided in Scenario B.

Guidance and Additional Instructions

If you answered "Yes" to Question 3, then proceed to Question 4 and Question 5 to determine whether your research meets the criteria for a clinical trial or an NIH-defined Phase III clinical trial.

If you answered "No," then you need to consider an alternative scenario. Return to the Decision Table.

CLINICAL TRIAL

Question 4: Does your proposed research include a clinical trial?

The NIH defines a *clinical trial* as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.

Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits these criteria of a clinical trial.

Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision-making for the subject or the test itself imposes more than minimal risk for subjects.

Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

Phase I clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range, and to identify side effects).

Phase II clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.

Phase III studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

Phase IV studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

Guidance and Additional Instructions

If you answered “Yes” to Question 4, then you will need to provide a general description of a Data and Safety Monitoring Plan. See Scenario E.

Also continue to Question 5 to determine whether your research meets the criteria for an NIH-defined Phase III clinical trial.

If you answered “Yes” to Question 3 (Clinical Research) and “No” to Question 4 (Clinical Trial), then follow the instructions for Scenario D.

If you answered “No” to Question 4, you will need to consider an alternative scenario. Return to the Decision Table.

NIH-DEFINED PHASE III CLINICAL TRIAL

Question 5: Does your proposed research meet criteria for an NIH-Defined Phase III Clinical Trial?

An *NIH-Defined Phase III Clinical Trial* is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of either evaluating an experimental intervention in comparison with a standard or control intervention or of comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

If your research meets the above criteria, then in addition to providing a Data and Safety Monitoring Plan, you will be expected to address whether you expect to find clinically important sex/gender and/or race/ethnicity differences in the intervention effect. The discussion may include supporting evidence and/or data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology, and other relevant studies.

You will be expected to provide a research plan that must include one of the following plans:

- Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, OR
- Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender and racial/ethnic groups is not required as subject selection criteria, but inclusion is encouraged.), OR
- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups.

Guidance and Additional Instructions

If you answered “Yes” to Question 5, then follow the instructions for Scenario F.

If you answered “No,” then you need to consider an alternative scenario. Return to the Decision Table.

EXEMPTION 4 GUIDANCE AND INFORMATION

Research that meets the criteria for Exemption 4 is Human Subjects Research but it is not considered clinical research.

Exemption 4 includes research projects involving the collection or study of *existing* data, documents, records, pathological specimens, or diagnostic specimens, if these sources are *publicly available* or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through *identifiers* linked to the subjects.

What is meant by "existing" data or specimens?

Exemption 4 applies to retrospective studies of specimens and/or data that have already been collected. The materials must be "on the shelf" (or in the freezer) at the time the protocol is submitted to the IRB or other designated officials at your institution to determine whether the research is indeed exempt. Research that involves the ongoing collection of specimens and/or data does not meet the criteria for Exemption 4.

What is meant by "publicly available sources"?

This language in the regulation was intended to apply to public sources of data, such as census data. Its meaning with respect to human tissue specimens is widely debated. Although there are organizations that make human cells and tissues broadly accessible to the research community, these materials are not usually available to the public at large and are not generally considered to be publicly available.

What is meant by "identifiers linked to the subjects"?

Identifiers, such as names, social security numbers, medical record numbers, or pathology accession numbers, or other codes that permit specimens to be linked to living individuals and perhaps also to associated medical information.

How can I determine whether my research meets the criteria for Exemption 4?

The humans subjects regulations decision charts (http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm) from the Office of Human Research Protection (OHRP) will help you to see whether your research falls under the human subjects regulations and if so, whether a research project meets the criteria for Exemption 4.

OHRP advises that investigators should not have the authority to make an independent determination that research involving human subjects is exempt. OHRP guidance states that Exemptions should be independently determined (http://www.hhs.gov/ohrp/humansubjects/guidance/irb71102.pdf). Institutions often designate their IRB to make this determination. Because NIH does not require IRB approval at time of application, the exemptions designated in item 4a often represent the opinion of the principal investigator, and the justification(s) provided by the principal investigator for the exemption(s) is/are evaluated during peer review.

Information is also available on the NIH Office of Extramural Research website at http://grants.nih.gov/grants/policy/hs/index.htm.

How can you determine whether research that involves only the use of specimens and/or data from pathology archives or a specimen bank and/or data repository is human subjects research?

The research described in your application may include more than one research project; thus the application may include separate projects that meet the requirements for either human subjects research, exempt human subjects research, or are not defined as human subjects research. Examples are provided below:

- If the specimens and/or data were obtained specifically for the currently proposed research project through intervention or interaction with a living individual, then your research is human subjects research.
- If you receive or have access to individually identifiable specimens or data from living individuals (e.g., pathology or medical records), your proposed research is human subjects research.
- If you receive or have access to existing individually identifiable private information or identifiable specimens from living individuals (e.g., pathology or medical records), but you as the investigator or your collaborator record the information in such a manner that you cannot subsequently access or obtain direct or indirect identifiers that are linked to the subjects the research project that you conduct using data recorded in this manner meets the requirements of Exemption 4. If you will retain or can access any identifiers, the research project is not exempt under Exemption 4.
- If you are using specimens and/or data and neither you nor your collaborators can identify the subjects from whom the specimens and/or data were obtained either directly or indirectly through coding systems, the HHS human subjects regulations (45 C.F.R. Part 46) do not apply at all.
- If your research involves only coded private information/data or coded specimens, OHRP does not consider this research to involve human subjects as defined under the HHS Protection of Human Subjects Regulations (45 C.F.R. Part 46.102(f)) *if* the following conditions are *both* met:
    - the private information/data or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; *and*
    - the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
        (a) the key to decipher the code is destroyed before the research begins;
        (b) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased;
        (c) there are IRB approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; *or*
        (d) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

Guidance and Additional Instructions

If your research meets the criteria for Exemption 4, refer to Scenario B.

If you need to consider an alternative scenario, return to the Decision Table.

INSTRUCTIONS PERTAINING TO NON-EXEMPT HUMAN SUBJECTS RESEARCH

In your application narrative, create a section entitled “E. Human Subjects Research” immediately following the last entry in the Research Design and Methods section. Although no specific page limitation applies to this section of the application, be succinct. Scientific Review Groups will assess each application as being “acceptable” or “unacceptable” with regard to the protection of human subjects.

As the first entry, create a heading entitled “Protection of Human Subjects.” Use subheadings to address the issues listed under items 1-4 below.

If your research includes a clinical trial, address item 5 "Data and Safety Monitoring Plan."

Protection of Human Subjects

1. RISKS TO THE SUBJECTS

a. ***Human Subjects Involvement and Characteristics***

- Describe the proposed involvement of human subjects in the work outlined in the Research Design and Methods section.
- Describe the characteristics of the subject population, including their anticipated number, age range, and health status.
- Identify the criteria for inclusion or exclusion of any subpopulation.
- Explain the rationale for the involvement of special classes of subjects, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations.
- List any collaborating sites where human subjects research will be performed, and describe the role of those sites in performing the proposed research.

b. ***Sources of Materials***

- Describe the research material obtained from living human subjects in the form of specimens, records, or data.
- Describe any data that will be recorded on the human subjects involved in the project.
- Describe the linkages to subjects, and indicate who will have access to subject identities.
- Provide information about how the specimens, records, or data are collected and whether material or data will be collected specifically for your proposed research project.

c. ***Potential Risks***

- Describe the potential risks to subjects (physical, psychological, social, legal, or other), and assess their likelihood and seriousness to the subjects.
- Where appropriate, describe alternative treatments and procedures, including the risks and benefits of the alternative treatments and procedures to participants in the proposed research.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. ***Recruitment and Informed Consent***

- Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.

- Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. Informed consent document(s) need not be submitted to the PHS agencies unless requested.

b. ***Protection Against Risk***

- Describe planned procedures for protecting against or minimizing potential risks, including risks to confidentiality, and assess their likely effectiveness.

- Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a description of the plan for data and safety monitoring of the research and adverse event reporting to ensure the safety of subjects.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

- Discuss the potential benefits of the research to the subjects and others.

- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

- Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.

- Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

NOTE: Test articles (investigational new drugs, devices, or biologicals) including test articles that will be used for purposes or administered by routes that have not been approved for general use by the Food and Drug Administration (FDA) must be named. State whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the Food and Drug Administration, and/or the status of requests for an IND or IDE covering the proposed use of the test article in the research plan.

5. DATA AND SAFETY MONITORING PLAN

- If your research includes a clinical trial, create a section heading entitled "Data and Safety Monitoring Plan."

- Provide a general description of a monitoring plan that you plan to establish as the overall framework for data and safety monitoring. Describe the entity that will be responsible for monitoring and the process by which Adverse Events (AEs) will be reported to the Institutional Review Board (IRB), the funding I/C, the NIH Office of Biotechnology Activities (OBA), and the Food and Drug Administration (FDA) in accordance with Investigational New Drug (IND) or Investigational Device Exemption (IDE) regulations. Be succinct. Contact the FDA (http://www.fda.gov) and also see the following websites for more information related to IND and IDE requirements:

http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr312_01.html (IND)
http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr812_01.html (IDE)

- The frequency of monitoring will depend on potential risks, complexity, and the nature of the trial; therefore, a number of options for monitoring trials are available. These can include, but are not limited to, monitoring by a:

  a. Principal Investigator (required)

  b. Independent individual/Safety Officer

  c. Designated medical monitor

  d. Internal Committee or Board with explicit guidelines

  e. Data and Safety Monitoring Board (DSMB). NIH specifically requires the establishment of *Data and Safety Monitoring Boards* (DSMBs) for *multi-site* clinical trials involving interventions that entail potential *risk* to the participants, and generally for Phase III clinical trials. Although Phase I and Phase II clinical trials may also use DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate.

  f. Institutional Review Board (IRB - required)

- A detailed Data and Safety Monitoring Plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html). For additional guidance on creating this Plan, see the above reference.

Guidance and Additional Instructions

Proceed to Inclusion of Women and Minorities.

INCLUSION OF WOMEN AND MINORITIES

Create a section heading entitled "Inclusion of Women and Minorities" and place it immediately following the “Protection of Human Subjects” section. Although no specific page limitation applies to this section of the application, be succinct.

Scientific Review Groups will assess each application as being “acceptable” or “unacceptable” with regard to the protection of human subjects.

In this section of the Research Plan, address, at a minimum, the following four points:

1. The targeted/planned distribution of subjects by sex/gender and racial/ethnic groups for each proposed study or protocol using the format in the Targeted/Planned Enrollment Table. (Instructions for completing this table are provided below.) If you are using existing specimens and/or data that does not meet the criteria for Exemption 4 and you do not have access to information on the distribution of women and minorities, so state and explain the impact on the goals of the research as part of the rationale that inclusion is inappropriate (item 3 below). Alternatively, you may describe the women and minority composition of the population base from whom the specimens and/or data will be obtained. Include the Targeted/Planned Enrollment Table (MS Word or PDF) in this section.
2. A description of the subject selection criteria and rationale for selection of sex/gender and racial/ethnic group members in terms of the scientific objectives and proposed study design. The description may include, but is not limited to, information on the population characteristics of the disease or condition under study.
3. A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group (see examples below).
4. A description of proposed outreach programs for recruiting sex/gender and racial/ethnic group members as subjects.

Examples of acceptable justifications for exclusion of:

A. ***One gender:***

1. One gender is excluded from the study because:
   - inclusion of these individuals would be inappropriate with respect to their health;
   - the research question addressed is relevant to only one gender;
   - evidence from prior research strongly demonstrates no difference between genders;
   - sufficient data already exist with regard to the outcome of comparable studies in the excluded gender, and duplication is not needed in this study.
2. One gender is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects by gender (e.g., uniquely valuable stored specimens or existing datasets are single gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens).
3. Gender representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or data-sets with incomplete gender documentation are used), and this does not compromise the scientific objectives of the research.

B. ***Minority groups or subgroups:***

1. Some or all minority groups or subgroups are excluded from the study because:
   - Inclusion of these individuals would be inappropriate with respect to their health;
   - The research question addressed is relevant to only one racial or ethnic group;

- Evidence from prior research strongly demonstrates no differences between racial or ethnic groups on the outcome variables;
- A single minority group study is proposed to fill a research gap;
- Sufficient data already exists with regard to the outcome of comparable studies in the excluded racial or ethnic groups and duplication is not needed in this study.

2. Some minority groups or subgroups are excluded or poorly represented because the geographical location of the study has only limited numbers of these minority groups who would be eligible for the study, and the investigator has satisfactorily addressed this issue in terms of:
   - The size of the study;
   - The relevant characteristics of the disease, disorder or condition;
   - The feasibility of making a collaboration or consortium or other arrangements to include representation.
3. Some minority groups or subgroups are excluded or poorly represented because the purpose of the research constrains the applicant's selection of study subjects by race or ethnicity (e.g., uniquely valuable cohorts, stored specimens or existing datasets are of limited minority representation, very small numbers of subjects are involved, or overriding factors dictate selection of subjects, such as matching of transplant recipients or availability of rare surgical specimens).
4. Racial or ethnic origin of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens or data sets with incomplete racial or ethnic documentation are used) and this does not compromise the scientific objectives of the research.

Additional Instructions and Requirements When NIH-Defined Phase III Clinical Trials Are Proposed

If your proposed research includes an NIH-Defined Phase III Clinical Trial, the section on Inclusion of Women and Minorities also must address whether you expect to find clinically important sex/gender and/or race/ethnicity differences in the intervention effect. The discussion may include supporting evidence and/or data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies. Your discussion of expected sex/gender and/or race/ethnicity differences in intervention effect must include selection and discussion of one of the following analysis plans:

- Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, *or*
- Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender and racial/ethnic groups is not required as subject selection criteria, but inclusion is encouraged.), *or*
- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups.

Instructions for Completing the Targeted/Planned Enrollment Tables for Reporting Race and Ethnicity Data for Subjects in Clinical Research

A. New Applications and Clinical Research Studies begun after January 10, 2002:

All new clinical research studies should collect and report information on participants with respect to two categories of ethnicity and five categories of race. The new Inclusion Enrollment Report Table (MS Word or PDF) for reporting summary data on participants to NIH includes two categories of ethnicity and five categories of race and is based on recent changes by the Office of Management and Budget (OMB) regarding standards for data on race and ethnicity. Investigators should review the instructions and Frequently Asked Questions about using the new Enrollment Table format at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html.

When reporting these data in the aggregate, investigators should report: (a) the number of respondents in each ethnic category; (b) the number of respondents who selected only one category for each of the five racial categories; (c) the total number of respondents who selected multiple racial categories reported as the "number selecting more than one race," and (d) the number of respondents in each racial category who are Hispanic or Latino. Investigators may provide the detailed distributions, including all possible combinations, of multiple responses to the racial designations as additional information. However, more detailed items should be designed in a way that they can be aggregated into the required categories for reporting purposes.

For new applications and clinical research studies begun after January 10, 2002, use the Targeted/Planned Enrollment Table format (MS Word or PDF).

Provide the study title.

The '"Total Planned Enrollment" means the number of subjects that are expected to be enrolled during the entire period of the study and are needed to evaluate the research question The "Total Planned Enrollment" will be reported in two ways in the table: by "Ethnic Category" and by "Racial Categories."

"Ethnic Category": Provide the numeric distribution of the Total Planned Enrollment according to ethnicity and sex/gender in the top part of the table.

"Racial Categories": Provide the numeric distribution of the Total Planned Enrollment, this time by racial categories and sex/gender, in the bottom part of the table. Note that Hispanic is not a racial category.

If there is more than one study/protocol, provide a separate table for each.

List any proposed racial/ethnic subpopulations below the table.

How should I report race and ethnicity data when my research involves a foreign population?

Investigators are encouraged to design their data collection instruments in ways that allow respondent self-identification of their racial and ethnic affiliation. However, these items should be designed in a way that they can be aggregated into the required categories. Also, the investigator can report on any racial/ethnic subpopulations by listing this information in an attachment to the required table. This may be particularly useful when distinctive subpopulations are relevant to the scientific hypotheses being studied.

When completing the tables, investigators should asterisk and footnote the table indicating that data includes foreign participants. If the aggregated data only includes foreign participants, the investigator should provide information in one table with an asterisk and footnote. However, if the study includes both domestic and foreign participants, the investigator should complete two separate tables – one for domestic data and one for foreign data, with an asterisk and footnote accompanying the table with foreign data.

B. Clinical Research Studies begun before January 10, 2002:

If the proposed research uses existing data, then use the formats below for competing continuations and competing supplements. Investigators should review the instructions and Frequently Asked Questions about using the new Enrollment Table format at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html.

Competing Continuations:

For competing continuations involving the collection of new/additional clinical data, use the "Targeted/Planned Enrollment Table (MS Word or PDF)" and the instructions above. *Note:* If you choose to report information with the new Targeted/Planned Enrollment Table, you must continue to use this format for the remaining years of the project.

For competing continuations involving studies begun before January 10, 2002 that do not involve the collection of new/additional clinical data, the data on ethnicity/race and sex/gender may be presented in EITHER the Targeted/Planned Enrollment Table (MS Word or PDF) OR the 4/98 Version of the Inclusion Table (MS Word or PDF). If data were originally collected from study subjects using two questions (one about ethnicity and one about race) and subjects were given the option of selecting more than one race, then use the Targeted/Planned Enrollment Table. Otherwise, use the 4/98 Version of the Inclusion Table, which uses a combined race/ethnicity format with five categories.

Competing Supplements:

For competing supplemental applications involving studies begun before January 10, 2002, investigators may report ethnicity/race and sex/gender composition using EITHER the Inclusion Enrollment Report (MS Word or PDF) OR the 4/98 Version of the Inclusion Table (MS Word or PDF). If data are being collected using two questions (one about ethnicity and one about race) and subjects were given the option of selecting more than one race, then use the Targeted/Planned Enrollment Table. *Note:* If you choose to report information with the new Targeted/Planned Enrollment Table, you must continue to use this format for the remaining years of the project.

If data are being collected using one question that combines ethnicity and race, use the 4/98 Version of the Inclusion Table. For previously funded studies that used the 4/98 Version of the Inclusion Table the earlier reporting format is NOT directly transferable to the format.

C. What Inclusion/Enrollment Table Should Principal Investigators Use for Reporting Accrual Data to NIH? (New versus Old Table)

The following instructions apply to progress reports, whether submitted as part of a non-competing or competing application.

Guidelines for choosing the new Inclusion Enrollment Report Table versus the old Inclusion Table are as follows:

New Inclusion Enrollment Report (MS Word or PDF)

- Studies begun after January 10, 2002, must be designed to ask participants two questions, one about their ethnicity and one about their race, and investigators must use the new Inclusion Enrollment Report table format for reporting summary data to NIH.
- Principal investigators who started a study prior to January 10, 2002 using the old Inclusion Table format for reporting summary data to NIH may switch to the new Inclusion Enrollment Report format if they choose to do so, but they must also change their data collection methods to ask two questions (one about ethnicity and another about race) rather than one question (that combined race and ethnicity) for all participants enrolled in the study from that point on.
- For studies that began prior to January 10, 2002: When the study is submitted for competing continuation and plans to collect new/additional data, the principal investigator is required to change to the new standards for collecting data and use the new Inclusion Enrollment Report format for reporting data to NIH. In some cases, this will mean that principal investigators will need to re-ask study participants about

their race and ethnicity using the new two-question format. Note: principal investigators should not ask again about race and ethnicity if the subjects are no longer participating in the study.

Old Inclusion Table (4/98 Version) MS Word or PDF

- Studies begun prior to January 10, 2002 (and now in their non-competing Type 5 period) that were structured with one question about race and ethnicity may continue to report enrollment/accrual data to NIH based on the old form, i.e., using five categories of race/ethnicity. However, when they come in for competitive renewal, they will need to change to the new standards/new form for any additional data collection.
- Principal investigators should not switch to the new form if only one question about race and ethnicity is used in data collection.
- Sample of old Inclusion Table format: http://grants.nih.gov/grants/funding/women_min/InclusionOld_Form.pdf

Investigators who have questions about these choices should contact NIH program staff for advice.

Guidance and Additional Instructions

After you have completed the Inclusion of Women and Minorities section, proceed to Inclusion of Children.

INCLUSION OF CHILDREN

- Create a section entitled “Inclusion of Children” and place it immediately following the last entry in the Inclusion of Women and Minorities section.
- For the purpose of implementing these guidelines, a ***child*** is defined as an individual under the age of 21 years (for additional information see http://grants.nih.gov/grants/funding/children/children.htm and http://grants.nih.gov/grants/guide/notice-files/not98-024.html).
- Provide either a description of the plans to include children or, if children will be excluded from the proposed research, application, or proposal, then you must present an acceptable justification (see below) for the exclusion.
- If children are included, the description of the plan should include a rationale for selecting a specific age range of children. The plan also must include a description of the expertise of the investigative team for dealing with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.
- Scientific Review Groups will assess each application as being "acceptable" or "unacceptable" with regard to the age-appropriate inclusion or exclusion of children in the research project.
- When children are involved in research, the Additional Protections for Children Involved as Subjects in Research (45 C.F.R. 46 Subpart D) apply and must be addressed in the “Human Subjects Research and Protection from Risks” subheading.

Justifications for Exclusion of Children

For the purposes of this policy, all individuals under 21 are considered children; however, exclusion of any specific age group, such as individuals under 18, should be justified in this section.

It is expected that children will be included in all clinical research unless one or more of the following exclusionary circumstances can be fully justified:

1. The research topic to be studied is not relevant to children.
2. There are laws or regulations barring the inclusion of children in the research.
3. The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be needlessly redundant. Documentation of other studies justifying the exclusions should be provided. NIH program staff can be contacted for guidance on this issue if the information is not readily available.
4. A separate, age-specific study in children is warranted and preferable. Examples include:
   a. The condition is relatively rare in children, as compared to adults (in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition); or
   b. The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or
   c. Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages or different age-related metabolic processes). While this situation may represent a justification for excluding children in some instances, consideration should be given to taking these differences into account in the study design and

expanding the hypotheses tested, or the interventions planned, to allow inclusion of children rather than excluding them.

5. Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). Although children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.
6. Study designs are aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children).
7. Other special cases can be justified by the investigator and found acceptable to the review group and the Institute Director.

Guidance and Additional Instructions

See Policy on Inclusion of Children.

SCENARIO A: NO HUMAN SUBJECTS RESEARCH PROPOSED

Criterion:

If you are uncertain as to whether your research involves Human Subjects please read: Question 1: Does your proposed research involve human subjects?

Instructions:

Check the box marked “No” on the Face Page (item 4).

In your application narrative, create a heading labeled “E. Human Subjects Research” and place it immediately after the last entry in the Research Design and Methods section. Include the following statement below the heading: “No Human Subjects Research is proposed in this application.”

If your proposed research involves human specimens and/or data from subjects, please provide a justification for your claim that no human subjects are involved (see guidance under Question 1: Does your proposed research involves human subjects?).

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

Do not follow the instructions for Scenario A if research activities involving human subjects are planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution. You will need to consider an alternative scenario.

If you need to consider an alternative scenario return to the Decision Table.

SCENARIO B: HUMAN SUBJECTS RESEARCH CLAIMING EXEMPTION 4

Criteria:

Human Subjects Research	Yes
Exemption	4
Clinical Research	No
Clinical Trial	N/A
NIH-Defined Phase III Clinical Trial	N/A

Instructions and Required Information:

Although no specific page limitation applies to this section of the application, be succinct in your responses.

Check the box marked “Yes” on the Face Page (item 4). Check “’Yes” if activities involving human subjects are planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution. “Yes” should be checked even if the research is exempt from requirements in the Federal regulations for the protection of human subjects (45 C.F.R. 46).

Indicate that you are claiming Exemption 4 on the Face Page (item 4a) and enter “NA” for item 4b, since no assurance is needed.

In your application narrative, create a heading entitled “E. Human Subjects Research” and place it immediately after the last entry in the Research Design and Methods section. Include the following statement below the heading: “This Human Subjects Research falls under Exemption 4.”

Address the following three items in this new section:

1. Human Subjects Involvement and Characteristics:

a. Describe the proposed involvement of human subjects in the work outlined in the Research Design and Methods section.

b. Describe the characteristics of the subject population, including their anticipated number, age range, and health status. If the characteristics of the population are not available, then the applicant should indicate that the information is unknown.

c. Identify the criteria for inclusion or exclusion of any subpopulation.

d. Explain the rationale for the involvement of vulnerable populations, such as fetuses, neonates, pregnant women, children, institutionalized individuals, or others who may be considered vulnerable populations. Exemptions 1-6 do not apply to research involving prisoners or subjects who become prisoners (see 45 C.F.R. Part 46 Subpart C). Although Exemptions 1 and 3-6 apply to research involving children (see 45 C.F.R. Part 46 Subpart D), Exemption 2 can only be used for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

e. List any collaborating sites where human subjects research will be performed and describe the role of those sites in performing the proposed research.

2. Sources of Materials:

a. Describe the research material obtained from living human subjects in the form of specimens, records, or data.

b. Describe any data that will be recorded on the human subjects involved in the project.

c. Describe the linkages to subjects, and indicate who will have access to subject identities.

d. Provide information about when the specimens, records, or data were collected and whether new material or data will need to be collected specifically for your proposed research project.

3. Justification for Exemption:

a. Indicate that you are claiming Exemption 4.

b. Provide a justification for why your research meets the criteria for Exemption 4.

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

What types of research meet the criteria for Exemption 4? Research projects involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. Determining the appropriateness of Exemption 4 for research using specimens and data can be complex.

Note: Prospective collection of additional specimens does not meet the criteria for Exemption 4.

If you are uncertain as to whether your research meets the criteria for Exemption 4, refer to Exemption 4 Guidance and Information.

If you need to consider an alternative scenario, return to the Decision Table.

SCENARIO C: HUMAN SUBJECTS RESEARCH CLAIMING EXEMPTION 1,2,3,5, OR 6

Criteria:

Human Subjects Research	Yes
Exemption Claimed	1, 2, 3, 5, 6
Clinical Research	Yes
Clinical Trial	N/A
NIH-Defined Phase III Clinical Trial	N/A

Instructions and Required Information:

Although no specific page limitation applies to this section of the application, be succinct.

Check the box marked “Yes” for item 4 on the Face Page, check the box marked “Yes” for item 4a on the Face Page, enter the exemption number that you are claiming. Enter “NA” for item 4b, since no OHRP assurance number is needed for exempt research.

Although your research may be exempt from the IRB oversight provisions, it is still human subjects research, and you need to follow the instructions that are identified for each of the following topics and provide the information that is requested.

In your application narrative, create a heading entitled “E. Human Subjects Research” and place it immediately after the last entry in the Research Design and Methods section. Address the following items in this new section. Include the following statement below the heading: “This Human Subjects Research falls under Exemption(s) … .”

1. Human Subjects Involvement and Characteristics:

a. Describe the proposed involvement of human subjects in the work outlined in the Research Design and Methods section.

b. Describe the characteristics of the subject population, including their anticipated number, age range, and health status.

c. Identify the criteria for inclusion or exclusion of any subpopulation (e.g., men, women, children).

d. Explain the rationale for the involvement of vulnerable populations, such as fetuses, neonates, pregnant women, children, institutionalized individuals. Please note that research involving prisoners is not exempt under any category (see 45 C.F.R. 46 Subpart C).

e. List any collaborating sites where human subjects research will be performed and describe the role of those sites in performing the proposed research.

2. Sources of Materials:

a. Describe the sources of the research material obtained from living human subjects in the form of specimens, records, or data.

b. Describe any data that will be recorded on the human subjects involved in the project.

c. Describe the linkages to subjects and indicate who will have access to subject identities.

d. Provide information about when the specimens, records, or data were collected and whether new material or data will need to be collected specifically for your proposed research project.

3. Justification for Exemption(s)

In this section, identify which exemption(s) (1, 2, 3, 5, or 6) you are claiming. (If you are claiming Exemption 4 please refer to Scenario B and the appropriate instructions.) Justify why your research is appropriate for the exemption(s) that you have claimed.

4. Inclusion of Women and Minorities (click and follow instructions)

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study.

Create a section entitled “Inclusion of Women and Minorities” and place it immediately following the last entry in the “Human Subjects Research” section.

Describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants. See http://grants.nih.gov/grants/funding/women_min/women_min.htm.

Include the Targeted/Planned Enrollment Table (MS Word or PDF) here.

5. Inclusion of Children (click and follow instructions)

For the purpose of implementing these guidelines, a child is defined as an individual under the age of 21 years. (For additional information see http://grants.nih.gov/grants/funding/children/children.htm and http://grants.nih.gov/grants/guide/notice-files/not98-024.html.)

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

If you are uncertain as to whether your research meets the criteria for an exemption please read: Question 2: Does your proposed human subjects research meet the criteria for one or more of the exemptions in the HHS regulations?

If you need to consider an alternative Scenario, return to the Decision Table.

SCENARIO D: CLINICAL RESEARCH

Criteria

Human Subjects Research	Yes
Exemption	No
Clinical Research	Yes
Clinical Trial	No
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information:

Although no specific page limitation applies to this section of the application, be succinct.

Check the box marked “Yes” for item 4 on the Face Page, for item 4a check the box marked “No,” and for item 4b enter your OHRP assurance number in the space provided on the Face Page.

In your application narrative, create a section entitled “E. Human Subjects Research” immediately following the last entry in the Research Design and Methods section. Include the following statement below the heading: “This Human Subjects Research meets the definition of ‘Clinical Research.’”

Create a subheading for each of the following items, follow the instructions that are identified for each topic, and provide the information that is requested:

- ***Protection of Human Subjects*** (click and follow instructions)
- ***Inclusion of Women and Minorities*** (click and follow instructions)
  Targeted/Planned Enrollment Table (MS Word or PDF)
- ***Inclusion of Children*** (click and follow instructions)

If your application involves collaborating sites, provide the information identified above for each participating site.

Guidance and Additional Instructions

Research that meets the criteria for Exemption 4 is not considered clinical research.

Research that uses *existing (archived)* specimens or data that *can* be linked to living individuals must address the inclusion of women, minorities and children as identified above, unless the investigator does not have access to the information. The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

If you are uncertain as to whether your research meets the criteria for clinical research, read: Question 3: Does your proposed research include clinical research?

If you need to consider an alternative scenario, return to the Decision Table.

SCENARIO E. CLINICAL TRIALS

Criteria

Human Subjects Research	Yes
Exemption	No
Clinical Research	Yes
Clinical Trial	Yes
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information:

Check the box marked “Yes” for item 4 on the Face Page, for item 4a check the box marked “No,” and for item 4b enter your OHRP assurance number in the space provided.

In your application narrative, create a section entitled “E. Human Subjects Research” immediately following the last entry in the Research Design and Methods section. Include the following statement below the heading: “This Human Subjects Research meets the definition of a clinical trial.” Create a subheading for each of the following items, follow the instructions that are identified for each topic, and provide the information that is requested:

- ***Protection of Human Subjects*** (click and follow instructions)
- ***Data and Safety Monitoring Plan*** (click and follow instructions)
- ***Inclusion of Women and Minorities*** (click and follow instructions)
  Targeted/Planned Enrollment Table (MS Word or PDF)
- ***Inclusion of Children*** (click and follow instructions)

If your application involves collaborating sites, provide information for each of the issues identified above for each participating site.

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research. If you are uncertain as to whether your research includes a clinical trial please read: Question 4: Does your proposed research include a clinical trial? If you need to consider an alternative scenario, return to the Decision Table.

SCENARIO F. NIH-DEFINED PHASE III CLINICAL TRIAL

Criteria

Human Subjects Research:	Yes
Exempt:	No
Clinical Research:	Yes
Clinical Trial:	Yes
NIH-Defined Phase III Clinical Trial:	Yes

Instructions and Required Information:

Check the box marked “Yes” for item 4 on the Face Page, for item 4a check the box marked “No,” and for item 4b enter your OHRP assurance number in the space provided.

In your application narrative, create a section entitled “E. Human Subjects Research” immediately following the last entry in the Research Design and Methods section. Include the following statement below the heading: “This Human Subjects Research is an NIH-defined Phase III Clinical Trial.”

Follow the instructions that are identified for each of the following topics and provide the information that is requested:

- ***Protection of Human Subjects*** (click and follow instructions)
- ***Data and Safety Monitoring Plan*** (click and follow instructions)
- ***Inclusion of Women and Minorities*** (click and follow instructions)
  Targeted/Planned Enrollment Table (MS Word or PDF)
- ***Inclusion of Children*** (click and follow instructions)

If your application involves collaborating sites, provide the information identified above for each participating site.

Guidance and Additional Instructions

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research. If you are uncertain as to whether your research includes clinical research, read Question 5: Does your proposed research meet criteria for an NIH-Defined Phase III Clinical Trial?

If you need to consider an alternative scenario, return to the Decision Table.

HUMAN SUBJECTS RESEARCH POLICY

Human Subjects Research Policy includes federal regulations for the protection of human subjects and the following NIH policies related to human subjects research.

PROTECTION OF HUMAN SUBJECTS

The Department of Health and Human Services (HHS) regulations for the protection of human subjects provide a systematic means, based on established, internationally recognized ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the HHS. The regulations stipulate that an applicant organization, whether domestic or foreign, bears responsibility for safeguarding the rights and welfare of human subjects in HHS-supported research activities. The regulations require that applicant organizations proposing to involve human subjects in nonexempt research, provide written Assurance of Compliance with the Office for Human Research Protections (OHRP), that they will comply with requirements set forth in the HHS regulations to protect human subjects. These regulations, 45 C.F.R. 46, Protection of Human Subjects, are available from OHRP, Department of Health and Human Services, The Tower Building, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852 or by contacting OHRP at ohrp@osophs.dhhs.gov, Telephone: 1-866-447-4777 or (301) 496-7005.

Under HHS regulations to protect human subjects from research risks, certain research areas are exempt. However, if an applicant makes inappropriate designations of the noninvolvement of human subjects or of exempt categories of research, this may result in delays in the review of an application or the return of the application without review. The PHS will make a final determination as to whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the Research Plan. When in doubt, consult with the Office for Human Research Protections (OHRP), Department of Health and Human Services by accessing their website http://www.hhs.gov/ohrp for guidance and further information.

No non-exempt research involving human subjects can be conducted under a HHS award unless that organization is operating in accord with an approved Assurance of Compliance and provides verification that an Institutional Review Board (IRB) that is registered under the specific Assurance has reviewed and approved the proposed activity in accordance with the HHS regulations. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the HHS regulations. Foreign applicant organizations must also comply with the provisions of the regulations.

In addition to the HHS human subjects regulations, FDA regulations (21 C.F.R. part 50; 21 C.F.R. part 56) may also apply to your research. FDA regulations generally apply to biomedical research involving an unapproved drug, device or biologic and may apply to certain studies of approved products. Researchers proposing such research should consult with their IRB and the FDA to determine whether and how the FDA regulations may apply. Additional information on FDA regulations is available at (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm).

Studies that involve the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human research participants (known as “human gene transfer” or “gene therapy”) are subject to the oversight and biosafety requirements outlined in the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) when these studies are conducted at, or sponsored by, an institution that receives any NIH support for recombinant DNA research. These requirements, which include review by an Institutional Biosafety Committee and submission to the NIH for review by the Recombinant DNA Advisory Committee, are described in Section III-C-1 and Appendix M of the NIH Guidelines (accessible at: http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html). Additional information on the special requirements that pertain to human gene transfer can be found in a series of Frequently Asked Questions at: http://www4.od.nih.gov/oba/RAC/RAC_FAQs.htm.

Federal requirements to protect human subjects apply to most research on human specimens (such as cells, blood, and urine), residual diagnostic specimens and medical information. Research involving the collection or study of existing data, documents, records, pathological specimens, diagnostic specimens, or tissues that are individually identifiable is considered “research involving human subjects.” The NIH Office of Extramural Research Human Subjects website contains additional information and Frequently Asked Questions that is available to help

investigators understand how these federal requirements apply to their research. See http://grants.nih.gov/grants/policy/hs/index.htm.

The HHS regulations also require "Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency" (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.120). This independent evaluation is conducted at the NIH through the peer review system and NIH staff review, and, as required, will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. On the basis of this evaluation, the NIH may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

VULNERABLE POPULATIONS

Investigators who conduct research involving pregnant women, human fetuses and neonates, prisoners, or children must follow the provisions of the regulations in Subparts B, C, and D of 45 C.F.R. Part 46, respectively, which describe the additional protections required for these populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins. Relevant information may be obtained at the OHRP website (http://www.hhs.gov/ohrp/policy/index.html).

REMINDER: HHS regulations at 45 C.F.R. Part 46, subpart C describe requirements for additional protections for research involving prisoners as subjects *or* individuals who become prisoners after the research has started. Refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/prisoner.htm for complete instructions.

Exemptions 1-6 do not apply to research involving prisoners or subjects who become prisoners (see Subpart C). Although Exemptions 1 and 3-6 apply to research involving children (see Subpart D), Exemption 2 can only be used for educational tests or research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

DATA AND SAFETY MONITORING PLANS FOR CLINICAL TRIALS

For each proposed clinical trial, NIH requires a data and safety monitoring plan that describes oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. A detailed data and safety monitoring plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects. The reporting of Adverse Events must be reported to the IRB, the NIH funding Institute or Center, and other required entities. This policy requirement is in addition to any monitoring requirements imposed by 45 C.F.R. Part 46. NIH requires the establishment of a Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials.

RESEARCH ON TRANSPLANTATION OF HUMAN FETAL TISSUE

In signing the application Face Page, the duly authorized representative of the applicant organization certifies that if research on the transplantation of human fetal tissue is conducted, the applicant organization will make available, for audit by the Secretary, HHS, the physician statements and informed consents required by section 498A (b)(2) and (c) of the Public Health Service Act, 42 U.S.C. 289g (b)(2) and (c), or ensure HHS access to those records, if maintained by an entity other than the applicant organization.

RESEARCH USING HUMAN EMBRYONIC STEM CELLS

http://stemcells.nih.gov/index.asp

In signing the application Face Page, the duly authorized representative of the applicant organization certifies that if research using human embryonic stem cells is proposed, the applicant organization will be in compliance with the "Notice of Extended Receipt Date and Supplemental Information Guidance for Applications Requesting

Funding that Proposes Research with Human Embryonic Stem Cells" (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-006.html).

IRB APPROVAL

NIH does not require certification of IRB approval of the proposed research prior to NIH peer review of an application. See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-031.html.

Following NIH peer review, applicants and their institutions will be notified of the need for review and approval of the proposed research by an OHRP-registered IRB. See http://www.hhs.gov/ohrp to register an IRB. Documentation of IRB approval must be sent to the Grants Management Office identified in the notice requesting certification. This IRB certification must include: the PHS application number, title of the project, name of the principal investigator/program director, date of IRB approval, and appropriate signatures. You may also use the optional form "Protection of Human Subjects - Assurance Identification/IRB Certification/Declaration of Exemption (Common Rule) (OMB Form No. 0990-0263) to meet this requirement: http://www.hhs.gov/ohrp/humansubjects/assurance/OF310.rtf

An institution is automatically considered to be engaged in human subjects research when it receives an NIH award to support nonexempt human subjects research. All institutions engaged in human subjects research must obtain a Federal Wide Assurance (FWA) from OHRP. Instructions for applying for a Federal Wide Assurance (FWA) are available from the OHRP website at http://www.hhs.gov/ohrp/assurances/assurances_index.html.

Any modifications in the Research Plan section of the application, required by either NIH or by the IRB must be submitted with the follow-up certification of IRB approval to the NIH before the competing award is made. It is the responsibility of the principal investigator/program director and the applicant organization to submit the follow-up certification.

If a year will have elapsed between the initial IRB review date and the anticipated award date, the awarding unit staff shall require re-review by the IRB prior to award.

REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

NIH requires education on the protection of human research participants for all individuals identified as Key Personnel before funds are awarded for applications or contract proposals involving human subjects. For information relating to this requirement, see the following see the following notices (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html), and Frequently Asked Questions found at: http://grants.nih.gov/grants/policy/hs_educ_faq.htm. Prior to award, applicants will be required to provide a description of education completed in the protection of human subjects for all Key Personnel involved in human subjects research. Although NIH does not endorse programs, there are curricula available that can provide guidance or that can be modified to provide training in this area. See http://ohsr.od.nih.gov/ for computer-based training developed for NIH that can be downloaded at no charge. For information on facilitating education and developing curricula, see http://www.nih.gov/sigs/bioethics.

RELEVANT POLICIES AND INFORMATION

PROCEDURES FOR SUBMISSION OF COMPLIANCE DOCUMENTS TO THE HUMAN PLURIPOTENT STEM CELL REVIEW GROUP FOR THE RESEARCH USE OF HUMAN EMBRYONIC GERM CELLS	NOTICE: NOT-OD-02-049 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-049.html
GUIDANCE FOR INVESTIGATORS AND INSTITUTIONAL REVIEW BOARDS REGARDING RESEARCH INVOLVING HUMAN EMBRYONIC STEM CELLS, GERM CELLS AND STEM CELL-DERIVED TEST ARTICLES	NOTICE: NOT-OD-02-044 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-044.html

IMPLEMENTATION ISSUES FOR HUMAN EMBRYONIC STEM CELL RESEARCH - FREQUENTLY ASKED QUESTIONS	NOTICE: NOT-OD-02-014 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-014.html
FEDERAL GOVERNMENT CLEARANCES FOR RECEIPT OF INTERNATIONAL SHIPMENT OF HUMAN EMBRYONIC STEM CELLS	NOTICE: NOT-OD-02-013 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-013.html
NOTICE OF EXTENDED RECEIPT DATE AND SUPPLEMENTAL INFORMATION GUIDANCE FOR APPLICATIONS REQUESTING FUNDING THAT PROPOSES RESEARCH WITH HUMAN EMBRYONIC STEM CELLS	NOTICE: NOT-OD-02-006 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-006.html
NOTICE OF CRITERIA FOR FEDERAL FUNDING OF RESEARCH ON EXISTING HUMAN EMBRYONIC STEM CELLS AND ESTABLISHMENT OF NIH HUMAN EMBRYONIC STEM CELL REGISTRY	NOTICE: NOT-OD-02-005 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html
NIH FUNDING OF RESEARCH USING SPECIFIED EXISTING HUMAN EMBRYONIC STEM CELLS	NOTICE: NOT-OD-01-058 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-059.html

NIH POLICY ON THE INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made by the Director, NIH, upon the recommendation of an Institute/Center Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research. This policy applies to research subjects of all ages.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The research plan should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants. See http://grants.nih.gov/grants/funding/women_min/women_min.htm.

NIH POLICY ON INCLUSION OF CHILDREN

(See Definition of "child.")

Research involving children must comply with the NIH Policy and Guidelines on the Inclusion of Children in Clinical Research. The following excerpts provide the key policy statements. Investigators should obtain full copies of the Policy and Guidelines from NIH staff, or from the NIH grants Web site under http://grants.nih.gov/grants/funding/children/children.htm.

NIH policy requires that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH unless there are clear and compelling reasons not to include them. Therefore, proposals for clinical research must include a description of plans for including children. If children will be excluded from the research, the application or proposal must present an acceptable justification for the exclusion.

In addition, the involvement of children as subjects in research must be in compliance with all applicable subparts of 45 C.F.R. Part 46 as well as with other pertinent Federal laws and regulations.

Additionally, IRBs have special review requirements to protect the well-being of children who participate in research. These requirements relate to risk, benefit, parental/guardian consent, and assent by children, and to research involving children who are wards of the state or of another institution. The local IRB approves research that satisfies the conditions set forth in the regulations.

NIH POLICY ON REPORTING RACE AND ETHNICITY DATA: SUBJECTS IN CLINICAL RESEARCH

The Office of Management and Budget (OMB) (http://www.whitehouse.gov/omb/fedreg/ombdir15.html) defines minimum standards for maintaining, collecting and presenting data on race and ethnicity for all Federal reporting agencies (including NIH). The categories in this classification are social-political constructs and should not be interpreted as being anthropological in nature. The standards were revised in 1997 and now include two ethnic categories, "Hispanic or Latino" and "Not Hispanic or Latino." There are five racial categories: American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; and White. Reports of data on race and ethnicity shall use these categories. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. The following definitions apply to the minimum standards for the ethnic and racial categories.

Ethnic Categories:

Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, “Spanish origin,” can be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino

Racial Categories:

American Indian or Alaska Native: A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American: A person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Ethnic/Racial Subpopulations: In addition to OMB ethnic and racial categories, NIH uses the following definition for ethnic/racial subpopulations:

Subpopulations: Each ethnic/racial group contains subpopulations that are delimited by geographic origins, national origins, and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific origins and/or cultural heritage. Attention to subpopulations also applies to individuals who self identify with more than one race. These ethnic/racial combinations may have biomedical, behavioral, and/or social-cultural implications related to the scientific question under study. (http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm)

GUIDANCE ON COLLECTING RACE AND ETHNICITY DATA FROM STUDY SUBJECTS

When an investigator is planning to collect data on ethnicity and race, the categories identified above should be used. The collection of greater detail is encouraged, for example on ethnic/racial subpopulations. However, any collection that uses more detail must be designed in a way that data can be aggregated into these minimally required categories. Use self-report or self-identification to collect this information by asking two separate

questions – one on ethnicity and one on race. Collect ethnicity information first followed by the question on race and provide subjects with the option to select more than one racial category. An example of a format for collecting information from study subjects in the US and that meets the OMB requirements can be found in the Ethnic Origin and Race section of the Personal Data Form Page (MS Word or PDF) in the PHS 398.

See NIH Policy on Inclusion of Women and Minorities.

Collecting Data on Foreign Populations: If you are conducting clinical research outside of the US, you should design culturally sensitive and appropriate data collection items and instruments that allow subjects to self-identify their ethnic and racial affiliation in a culturally appropriate manner. These items, however, should be designed in a way that allow you, the investigator, to aggregate the information into the OMB minimally required ethnic and racial categories when reporting the information to NIH.

Submitting Applications or Proposals Using Existing Data in Clinical Research with No Plans for Collecting New/Additional Data:

Investigators are instructed to provide plans for the total number of subjects proposed for the study and to provide the distribution by ethnic/racial categories and sex/gender. Under these circumstances, investigators are not required to re-contact subjects solely to comply with the newly revised categories. If the existing data on ethnicity and race allow accurate correspondence with the new categories, the investigator can use the format in the Targeted/Planned Enrollment table (MS Word or PDF). However, if the existing data do not allow accurate correspondence with the new categories, information may be reported using the former categories and according to the format in the 4/98 Version of the Inclusion Table
http://grants.nih.gov/grants/funding/women_min/InclusionOld_Form.pdf

Annual Progress Reports (Type 5 applications) and Competing Supplement Applications

In annual Progress Reports, investigators conducting clinical research are required to provide the cumulative total enrollment of subjects to-date, showing the distribution by ethnic/racial categories and sex/gender on EITHER the new Inclusion Enrollment Report (MS Word or PDF) OR the format in the former 4/98 Version of the Inclusion Table (MS Word or PDF).

For competing supplement applications, any proposed additions to the Targeted/Planned Enrollment Table should be provided, in addition to the current Inclusion Enrollment Table.

If Data Collection is Ongoing, Such that New Subjects Will be Enrolled and/or Additional Data Will be Collected from Human Subjects:

Investigators may choose to report ethnicity/race and sex/gender sample composition using EITHER the new Inclusion Enrollment Report (MS Word or PDF) OR the format in the former 4/98 Version of the Inclusion Table (MS Word or PDF).

[Note: If investigators with on-going data collection choose to report information using the new Inclusion Enrollment Report, they must continue to use this format for the remaining years of the project.]

If Data Collection is Complete, Such that No New/Additional Subject Contact is Planned:

Investigators may EITHER continue to report using the former categories and according to the 4/98 Version of the Inclusion Table, OR, if data allow accurate correspondence with the new categories, use the format in the new Inclusion Enrollment Report.

Additional Information

Additional information on NIH policy regarding the Inclusion of Women and Minorities in Clinical Research can be found at the website http://grants.nih.gov/grants/funding/women_min/women_min.htm.